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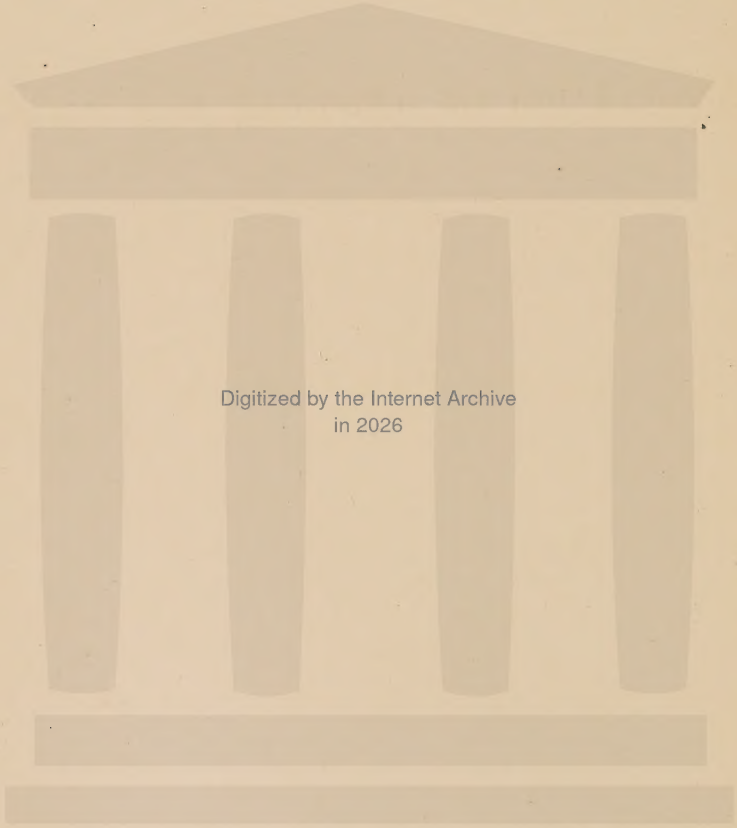
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OF THE

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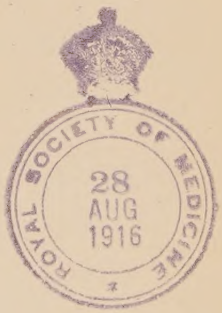
THIRTIETH SESSION

HELD AT WASHINGTON, D. C.

MAY 11, 12 AND 13, 1915

VOLUME XXX



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1915

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The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

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1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
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1909.	V. C. Vaughan.	Henry Hun.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
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*1886.	1915.	STERNBERG, GEORGE M., 2005 Massachusetts Ave., Washington.
*1886.	1915.	TRUDEAU, EDWARD L., Saranac Lake, N. Y.
*1886.	1915.	TYSON, JAMES, 1506 Spruce St., Philadelphia.
1889.	1915.	VAUGHAN, VICTOR C., Univ. of Michigan, Ann Arbor.
*1886.	1913.	WELCH, WILLIAM H., 807 St. Paul St., Baltimore.

EMERITUS MEMBERS

* Original Members

Elected Active Member	Elected Emeritus Member	
1888.	1910.	Bridge, Norman, 10 Chester Place, Los Angeles, Cal.
*1886.	1906.	Councilman, Wm. T., 78 Bay State Road, Boston.
1894.	1908.	Cutler, Elbridge G., 214 Beacon St., Boston.
1897.	1905.	Cushny, Arthur C., University of London, London, England.
*1886.	1905.	Edes, Robert T., 340 Summer Ave., Reading, Mass.
1890.	1902.	Fisk, S. A., Brimfield, Mass.
*1886.	1900.	Guitéras, John, Havana, Cuba.
*1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1897.	1910.	Hektoen, Ludvig, Rush Medical College, Chicago.
*1886.	1908.	Henry, Frederick P., 114 S. 18th St., Philadelphia.
1890.	1902.	Hurd, H. M., Johns Hopkins Hospital, Baltimore.
1899.	1914.	James, Walter B., 17 W. 54th St., New York.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
1901.	1913.	Morse, John L., 70 Bay Street Road, Boston.
1898.	1914.	Pfaff, Franz, Dresdner Bank, Berlin.
*1886.	1898.	Polk, Wm. M., 7 East 36th St., New York.
*1886.	1915.	Putnam, James J., 106 Marlborough St., Boston.
*1886.	1904.	Robinson, Beverley, 42 West 37th St., New York.
1900.	1914.	Sears, Geo. G., 19 Marlborough St., Boston, Mass.
*1886.	1912.	Shattuck, Frederick C., 135 Marlborough Street, Boston.
*1886.	1905.	Shattuck, George B., 183 Beacon St., Boston.
*1886.	1914.	Smith, A. A. 18 W. 51st Street, New York.
1887.	1902.	Starr, Louis, 1818 S. Rittenhouse Square, Phila.
1887.	1911.	Starr, M. Allen, 5 West 54th St., New York.
1889.	1904.	Walcott, Henry P., 11 Waterhouse St., Cambridge, Mass.

Elected Active Member	Elected Emeritus Member	
*1886.	1912.	Ward, Samuel B., 281 State St., Albany.
1898.	1915.	Wesbrook, F. F., Univ. British Columbia, Vancouver, B. C.
*1886.	1911.	Wilkins, George, 899 Dorchester St., Montreal.
*1886.	1911.	Wilson, James C., 1509 Walnut St., Philadelphia.
*1886.	1908.	Wood, Horatio C., 4107 Chester Ave., Philadelphia.
1899.	1912.	Wright, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston

DECEASED MEMBERS

* Original Members

Date of Election

*1886. Atkinson, I. E., Baltimore.
*1886. Ball, A. Brayton, New York.
1890. Barker, Fordyce, New York.
*1886. Baumgarten, G., St. Louis.
*1886. Billings, John S., New York.
*1886. Bowditch, Henry I., Boston.
*1886. Bruen, Edward T., Philadelphia.
*1886. Busey, Samuel C., Washington, D. C.
1907. Carroll, James, Washington, D. C.
*1886. Chew, Samuel C., Baltimore.
*1886. Clark, Alonzo, New York.
*1886. Clymer, Meredith, New York.
*1886. Da Costa, J. M., Philadelphia.
1889. Dabney, William C., University of Virginia.
*1886. Dalton, John C., New York.
*1886. Dana, Israel T., Portland, Maine.
1888. Danforth, I. N., Chicago.
*1886. Donaldson, Frank, Baltimore.
*1886. Draper, William H., New York.
1899. Ely, John Slade, New Haven, Conn.
1895. Fischel, William E., St. Louis.
*1886. Fitz, Reginald H., Boston.
*1886. Folsom, Chas. F., Boston.
*1886. Forchheimer, F., Cincinnati.
*1886. Formad, Henry F., Philadelphia.
1889. Geddings, W. H., Atken, S. C.
*1886. Graham, J. E., Toronto, Canada.
1898. Herter, C. A., New York.
*1886. Howard, R. Palmer, Montreal, Canada.
*1886. Hudson, E. Darwin, Jr., New York.
*1886. Hutchinson, James H., Philadelphia.
*1886. Janeway, E. G., New York.
*1886. Johnson, Hosmer A., Chicago.
1899. Johnston, W. G., Montreal, Canada.

Date of Election

*1886. Johnston, W. W., Washington, D. C.
1902. Kelly, A. O. J., Philadelphia.
*1886. Kinnicutt, Francis P., New York.
1890. Latimer, Thomas S., Baltimore.
*1886. Leidy, Joseph, Philadelphia.
*1886. Longstreth, Morris, Cambridge, Mass.
*1886. Loomis, Alfred L., New York.
1889. Loving, Starling, Columbus, O.
*1886. Lyman, Henry M., Chicago.
1890. MacDonnell, R. P., Montreal, Canada
*1886. McBride, Thomas A., New York.
1887. Meigs, Arthur V., Philadelphia.
*1886. Metcalfe, John T., Cold Spring, N. Y.
*1886. Miles, F. T., Baltimore.
*1886. Minot, Francis, Boston.
*1886. Mitchell, S. Weir, Philadelphia.
1887. Musser, John H., Philadelphia.
1898. Packard, Frederick A., Philadelphia.
*1886. Peabody, George L., Newport, R. I.
*1886. Pepper, William, Philadelphia.
1888. Prentiss, D. W., Washington, D. C.
1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo, N. Y.
1889. Roosevelt, J. West, New York.
*1886. Ross, George, Montreal, Canada.
1893. Rotch, Thomas M., Boston.
*1886. Schmidt, H. D., New Orleans.
*1886. Sinkler, Wharton, Philadelphia.
1891. Smith, Andrew H., New York.
1905. Steele, J. Dutton, Philadelphia.
1896. Stewart, D. D., Philadelphia.
*1886. Stewart, James, Montreal, Canada.
*1886. Stillé, Alfred, Philadelphia.
*1886. Thacher, James K., New Haven, Conn.
*1886. Whittaker, James T., Cincinnati.

ASSOCIATION

OF

AMERICAN PHYSICIANS

CONSTITUTION

As Amended May 15, 1912

ARTICLE I

OBJECT AND NAME

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

ARTICLE II

MEMBERS

The number of active members shall be limited to one hundred and sixty. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to emeritus membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of honorary members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

ARTICLE III

OFFICERS

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

ARTICLE IV

DUTY OF OFFICERS

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of TRANSACTIONS.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

ARTICLE V

COUNCIL

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate,

and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

ARTICLE VI

MEETINGS

1. The Association shall hold an annual meeting either in the City of Washington, D. C., or at Atlantic City at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. The President shall have complete charge of, and responsibility for, the program. He shall have power to accept or reject any paper offered. He shall have power to limit the number of papers, and to assign a time limit for each one. Papers shall be presented to the Association only in abstract, and preferably shall not be read from manuscript. They may be published in full in the TRANSACTIONS as also in any other medical publication.

5. The referee, co-referee, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

ARTICLE VII

QUORUM

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum, and for altering the Constitution twenty-five members shall be necessary.

ARTICLE VIII

ELECTION OF MEMBERS

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting

of the Association; and within six months of the time of nomination the nominators shall transmit to the Council letters stating the qualifications of the nominee and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The elections of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

ARTICLE IX

ANNUAL DUES

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

ARTICLE X

AMENDMENTS TO THE CONSTITUTION

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

THIRTIETH ANNUAL MEETING

Held at Washington, D. C., May 11, 12, *and* 13, 1915

The following members were present at the meeting:

Abbott, A. C.
Abel, J. J.
Adams, S. S.
Anderson, J. F.
Ashford, B. K.
Babcock, R. H.
Baldwin, E. R.
Barker, L. F.
Bass, C. C.
Biggs, H. M.
Billings, Frank
Boggs, T. R.
Bolton, B. M.
Brill, N. E.
Brown, Lawrason
Brown, T. R.
Brown, P. K.
Cabot, R. C.
Camac, C. N. B.
Cannon, W. B.
Capps, J. A.
Christian, H. A.
Cohen, S. Solis
Cole, R. I.
Collins, Joseph
Conner, L. A.
Coplin, W. M. L.
Councilman, W. T.
Dock, George
Ford, W. W.
Freeman, R. G.
Friedenwald, J.
Fussell, M. H.
Futcher, T. B.
Greene, C. L.
Griffith, J. P. C.
Hamilton, W. F.
Hamman, L. V.
Herrick, J. B.
Holt, L. E.
Hoover, C. F.
Howard, W. T.
Howland, John
Hun, Henry
Hunt, Reid
Jacobi, A.
Janeway, T. C.
Joslin, E. P.
Kinyoun, J. J.
Klotz, Oskar
Kober, G. M.
Koplik, Henry
Lafleur, H. A.
Lambert, S. W.
Landis, H. R. M.
Lewis, M. J.
Libman, E.
Longcope, W. T.
McCrae, Thomas
McPhedran, A.
MacCallum, W. G.
Meltzer, S. J.
Meyer, Adolph
Miller, J. L.
Mitchell, J. K.
Morris, R. S.
Norris, G. W.
Northrup, W. P.
Opie, E. L.

Ordway, Thomas
Park, W. H.
Peabody, F. W.
Pearce, R. M.
Pemberton, R.
Plummer, H. S.
Pratt, J. H.
Preble, R. B.
Richardson, M. W.
Riesman, David
Robinson, G. C.
Rosenau, M. J.
Rous, Peyton
Rowntree, L. G.
Sailer, Joseph
Sewall, Henry
Sippy, B. W.
Smith, Elsworth
Sollman, T. H.
Stengel, Alfred
Stockton, C. C.
Taylor, A. E.
Thayer, W. S.
Tyson, James
Vickery, H. F.
Wadsworth, A. B.
Welch, Wm. H.
Wells, H. G.
White, F. W.
White, Wm. C.
Williams, F. H.
Wilson, Jas. C.
Wilson, L. B.
Wood, E. R.
Wood, F. C.
Woodyatt, R. T.

Tuesday, May 11

Morning Session.—The Association was called to order by the President, Dr. S. J. Meltzer, at 10 A.M., who delivered the President's address.

The Treasurer presented his annual report, showing receipts to have been $2679.81; expenditures, $2058.83; leaving a balance of $620.98 in the Treasury. The report was referred to an auditing committee composed of Drs. Jos. L. Miller and Wm. H. Park.

The Secretary presented the following recommendations from the Council:

Resolved, That for the ensuing year the annual dues shall be $5 for salaried Laboratory Workers; $7.50 for Associate Members; $15 for Practitioners.

That the Transactions of the Association to Emeritus Members shall be $4 a volume.

The Council also recommends that a time limit be placed, viz., October 15, within which contributions may be received for publication in the Transactions, and that authors are expected to pay for any material alterations after the manuscript has been set up in galley proof.

The Council recommends that the Medical Department of the Columbia University and the Medical Society of the State of Rhode Island be placed on the mailing list to receive the Transactions.

The Council recommends the election of the following officers for the ensuing year and also the election of the following nominees for Honorary, Active, and Associate Members:

President—Henry Sewall.

Vice-President—George Dock.

Secretary—George M. Kober.

Recorder—Thomas McCrae.

Treasurer—J. P. Crozer Griffith.

Councillor—Herbert C. Moffitt.

Representative on the Executive Committee of the American Congress of Physicians and Surgeons—Theodore C. Janeway.

Alternative Representative—Richard P. Strong.

Honorary Members—Francis A. Delafield, Henry Hun, George M. Sternberg, Edward L. Trudeau, James Tyson, Victor C. Vaughan.

Active Members.—Nathan E. Brill, New York; Joseph Erlanger, St. Louis; Charles P. Emerson, Indianapolis; Louis V. Hamman, Baltimore; Oskar Klotz, Pittsburgh; H. R. M. Landis, Philadelphia; Roger S. Morris, Cincinnati; Hideyo Noguchi, New York; G. Canby Robinson, St. Louis; Leonard G. Rowntree, Baltimore; Elmer E. Southard, Boston; Wm. Charles White, Pittsburgh.

Associate Members.—Alfred E. Cohn, New York; Max Einhorn, New York; Nellis B. Foster, New York; Channing Frothingham, Boston; Ernest E. Irons, Chicago; James W. Jobling, Nashville; Roger I. Lee, Boston; James Alex. Miller, New York; Homer F. Swift, New York; S. Burt Wolbach, Boston.

Dr. James Tyson, as chairman of the committee appointed to coöperate with the George Washington Memorial Association to raise funds, reported that $200 have been collected and $125 have been subscribed subject to a general response. In view of discouraging facts, the committee, composed of Drs. James Tyson, F. C. Shattuck, and Frank Billings, are unanimous in recommending that the project be given up and the subscriptions already paid and in the hands of the Treasurer be returned to the donors.

The Secretary expressed the hope that the good work would go on, as the project not only involved a suitable memorial to the father of our country, but also a dignified home for all national scientific societies.

Dr. Francis W. Peabody read a paper entitled, "Observations on Dyspnea in Cardiac Diseases."

Dr. W. S. Thayer presented a communication on "Stokes-Adams Syndrome, with a Remarkable Delay in the As–Vs Conduction Time."

Dr. Alfred E. Cohn, by invitation, read a paper on "The Present Status of the Electrocardiographic Method in Clinical Medicine."

These papers were discussed by Drs. L. F. Barker and Jas. B. Herrick, and the discussion was closed by Dr. Cohn.

Dr. Thomas R. Brown presented a paper on "The Physiology and Pathology of the Duodenal Mucous Membrane."

Dr. Franklin W. White presented a communication entitled, "Observations on the Use of the Duodenal Tube for Diagnosis and Treatment."

Dr. William J. Mayo, by invitation, presented a paper on "Chronic Duodenal Ulcer."

Dr. Frank Billings, who was on the program for a paper on "Chronic Duodenal Ulcer," relinquished his time to Dr. B. W. Sippy, who presented a paper on the "Medical Cure of Gastric and Duodenal Ulcer by Means of Efficient Removal of Gastric Juice Corrosion."

These papers were discussed by Drs. L. F. Barker, Wm. H. Welch, Frank Billings, Alex. McPhedran, E. Libman, J. Friedenwald, C. F. Hoover, S. Solis Cohen, Louis B. Wilson, and H. G. Wells. The discussion was closed by Dr. Wm. J. Mayo.

Dr. Francis R. Wood presented "A Review of the Advances in our Knowledge and Treatment of Cancer in the last Thirty Years."

Dr. Francis H. Williams presented several radiographs, with a case "Illustrating Some of the Limitations of Physical Examination of the Thorax and also Those of an *X*-ray Examination." This paper was discussed by Drs. Henry Sewall and Theodore C. Janeway.

Adjourned at 1.10 P.M.

Afternoon Session.—The Association reassembled at 2.30 and was called to order by the President.

Dr. L. G. Rowntree presented a joint contribution by himself, N. Keith, and J. F. Geraghty, entitled "A Method for Determining Total Plasma and Blood Volume."

Dr. L. G. Rowntree also presented a joint contribution by himself, McKim Marriott, and R. L. Levy entitled, "A Simple Method of Determining Variations in the H-ion Concentration of the Blood."

Dr. N. E. Brill presented a "Report of a Case of Pernicious Anemia with an Unusual Blood Condition."

Dr. George Dock presented "A Report of a Case with Sickle-shaped Red-blood Corpuscles," by himself, Dr. J. E. Cook, and Jerome Meyer.

Dr. R. M. Pearce presented a joint contribution by Samuel Goldschmidt, O. H. Perry Pepper, and Dr. Pearce, entitled, "Metabolism Studies Before and After Splenectomy in Congenital Hemolytic Jaundice."

Dr. J. J. Abel presented a joint contribution "On Plasmaphaeresis," by J. J. Abel, B. B. Turner, E. K. Marshall, Jr., and P. D. Lamson.

Dr. Peyton Rous presented a paper on "The Preservation in Vitro of Living Erythrocytes," by Peyton Rous and J. R. Turner.

Dr. E. Libman presented "Clinical Studies in Blood Transfusion," by himself and R. Ottenberg.

The papers were discussed by Drs. Richard C. Cabot, Jos. L. Miller, R. Weil, Theodore C. Janeway, J. J. Abel, Peyton Rous, W. S. Thayer, E. Libman, and N. E. Brill.

Dr. Wm. H. Park presented a communication on "The Progress Achieved during the Last Thirty Years in the Treatment and Prevention of Diphtheria."

Dr. Matthias Nicoll, Jr., by invitation, read a paper on "The Treatment of Tetanus with Antitoxin given Intraspinally."

Dr. Rufus Cole read a paper entitled, "The Treatment of Acute Lobar Pneumonia by Specific Methods."

No discussion.

Dr. Warfield T. Longcope presented a communication entitled, "The Relationship of Chronic Protein Intoxication in Animals to Anaphylaxis."

No discussion.

Dr. W. S. Thayer presented the following amendment to Article II of the Constitution, relating to the membership of the Association, which is as follows:

Provided, That in any case of removal of an active member to a locality so distant that his attendance at the annual meetings may reasonably be regarded as impossible, the Council may be empowered, should it so desire, to transfer the name of such a member to the list of Emeritus Members without regard to the length of his previous active membership.

W. T. Longcope,
Joseph Sailer,
Reid Hunt,
E. L. Opie,
Henry A. Christian.

Adjourned at 4.45 P.M.

Wednesday, May 12

Morning Session.—The Association was called to order at 9.15.

Dr. Joseph L. Miller, on behalf of the Auditing Committee, reported that the books and accounts of the Treasurer have been examined and found correct.

Dr. James Tyson, chairman of the committee to coöperate with the George Washington Memorial Association, asked for specific instructions, and upon motion of Dr. Kober the committee was continued, with power to invest the funds now in hand.

The President appointed Drs. S. Solis Cohen and Rufus Cole as tellers for the election of officers and members, and the following were elected:

President—Henry Sewall.
Vice-President—George Dock.
Secretary—George M. Kober.
Recorder—Thomas McCrae.
Treasurer—J. P. Crozer Griffith.
Councillor—Herbert C. Moffitt.
Representative on the Executive Committee of the American Congress of Physicians and Surgeons—Theodore C. Janeway.
Alternate Representative—Richard P. Strong.
Honorary Members—Francis A. Delafield, Henry Hun, George M. Sternberg, Edward L. Trudeau, James Tyson, Victor C. Vaughan.

Active Members.—Nathan E. Brill, New York; Joseph Erlanger, St. Louis; Charles P. Emerson, Indianapolis; Louis V. Hamman, Baltimore; Oskar Klotz, Pittsburgh; H. R. M. Landis, Philadelphia; Roger S. Morris, Cincinnati; Hideyo Noguchi, New York; G. Canby Robinson, St. Louis; Leonard G. Rowntree, Baltimore; Elmer E. Southard, Boston; Wm. Charles White, Pittsburgh.

Associate Members.—Alfred E. Cohn, New York; Max Einhorn, New York; Nellis B. Foster, New York; Channing Frothingham, Boston; Ernest E. Irons, Chicago; James W. Jobling, Nashville; Roger I. Lee, Boston; James Alex. Miller, New York; Homer F. Swift, New York; S. Burt Wolbach, Boston.

Dr. Henry Sewall presented a joint contribution, with Dr. Cuthbert Powell, entitled, "Studies on the Relations of Hypersusceptibility and Insusceptibility Induced in Guinea-pigs by the Instillation of Horse Serum into the Nose."

Dr. Walter B. Cannon, with Dr. R. Fitz, presented a contribution entitled, "Pathological Changes Arising from Overaction of the Cervical Sympathetic."

These papers were discussed by Drs. R. Weil, S. Solis Cohen, and the discussion was closed by Drs. Sewall and Cannon.

Dr. Henry A. Christian presented a contribution entitled, "Studies of Nephritis," with the collaboration of Drs. Channing Frothingham, Jr., James P. O'Hare, and Allen C. Woods. The studies cover the following: (*a*) Test renal meals in relation to renal function. (*b*) Quantitative studies of the non-proteid nitrogenous bodies of the blood. (*c*) Diuresis in relation to diuretics. (*d*) Functional tests in relation to anatomical changes in the kidney.

Dr. Samuel W. Lambert presented a joint paper, with Dr. Henry S. Patterson, on "Poisoning with Bichloride of Mercury and its Treatment."

Dr. L. A. Conner presented, for Dr. Nellis B. Foster, a paper entitled, "The Isolation of a Toxic Substance from the Blood of Uremic Patients."

These papers were discussed by Drs. Tyson, McCrae, Fussell, Rosenthal, Rowntree, Janeway, and Jacobi, and the discussion was closed by Drs. Christian, Lambert, and L. A. Conner.

Dr. Frederick M. Allen, by invitation, presented a paper on "Long Fasting in Diabetes."

Dr. E. P. Joslin read a paper on the "Present-day Treatment and Prognosis in Diabetes."

Dr. David Riesman read a paper on "Mild Diabetes in Children."

Dr. A. A. Epstein presented a paper by himself and Dr. S. Baehr entitled, "Studies in Experimental Pancreatic Diabetes."

These papers were discussed by Drs. Frank Billings, Henry Koplik, A. E. Taylor, Henry A. Christian, L. F. Barker, R. T. Woodyatt, E. Libman, L. A. Conner. The discussion was closed by Dr. Frederick M. Allen, Dr. E. P. Joslin, and Dr. A. A. Epstein.

Dr. Joseph L. Miller read a paper on "The Actual Value of Symptomatic Treatment," which was discussed by Drs. S. Solis Cohen, George Dock, and A. Jacobi.

Adjourned at 1.15 P.M.

Afternoon Session.—The Association reassembled at 2.30, and was called to order by the President.

Dr. C. F. Hoover read a paper on "The Significance of Acroataxia and Proximal Ataxia of the Extremities in Differentiating between Disease of the Peripheral Nerves and Spinal Cord Disease."

Dr. W. W. Ford read a paper on "The Present Status of Hygiene or Public Health and its Future in America."

This paper was discussed by Drs. M. J. Rosenau, John F. Anderson, G. M. Kober, and Alex. C. Abbott.

Dr. John F. Anderson presented a communication entitled, "The Alleged Relation between Vaccine Virus and Post-vaccination Tetanus."

This paper was discussed by Dr. George Dock, M. J. Rosenau, and the discussion was closed by Dr. Anderson.

Dr. C. C. Bass read a paper on "Recent Application on Chemotherapy, with Special Reference to the Action of Emetin upon Endameba Buccalis, the Specific Cause of Alveolodental Pyorrhea."

This paper was discussed by Drs. C. N. B. Camac and L. G. Rowntree, and the discussion was closed by Dr. Bass.

Dr. Joseph H. Pratt presented a paper entitled, "Studies on the Uric Acid Metabolism in Gout," which was not discussed.

Dr. Rowland G. Freeman read a paper on the "Open-air Treatment of Pneumonia and Anemia in Children."

Dr. S. Solis Cohen read "A Brief Note on the Value of Pituitary Preparations (Posterior Lobe) in Acute Lobar Pneumonia."

The last two papers were discussed by Drs. W. P. Northrup, Alex. McPhedran, and the discussion was closed by Dr. S. S. Cohen.

Dr. Louis B. Wilson presented a joint contribution by himself and Dr. Edward C. Kendall entitled, "The Relationship of the Pathological Histology and the Iodine Compounds of Human Thyroids."

Dr. Edward C. Kendall, by invitation, presented a contribution on "The Isolation in Crystalline Form of the Iodine-containing Compound Occurring in the Thyroid, its Chemical Nature and Physiological Activity."

Dr. H. S. Plummer read a paper on "The Blood-pressure in Thyrotoxicosis."

These papers were discussed by Dr. C. F. Hoover, and the discussion was closed by Drs. L. B. Wilson and H. S. Plummer.

Dr. Joseph Collins presented a communication entitled, "Pathognomonic Changes of the Cerebrospinal Fluid in Nervous Diseases," which was discussed by Dr. B. W. Sippy.

Dr. Joseph A. Capps presented a communication entitled, "Further Observations on Pain in Diaphragmatic Pleurisy," which was not discussed.

Adjourned at 5.55 P.M.

Thursday, May 13

Morning Session.—The Association was called to order at 9.30.

Dr. M. Howard Fussell presented "A Case of Herter's Infantilism" (illustrated with lantern slides), which was not discussed.

Dr. L. F. Barker presented a joint contribution entitled, "Clinical Studies of Several Types of Acute Leukemic States," by L. F. Barker, W. A. Baetger, and Sidney Miller."

This paper was discussed by Drs. Jos. L. Miller, Ordway, Billings, Herrick, Stengel, Meltzer, and Dock, and the discussion was closed by Dr. L. F. Barker.

Drs. Thomas McCrae and W. M. L. Coplin presented a contribution entitled, "Colloid Carcinoma of the Peritoneum" (illustrated with lantern slides).

This paper was discussed by Drs. Louis B. Wilson, David Riesman, and Stengel. The discussion was closed by Drs. McCrae and Coplin.

Dr. Elsworth S. Smith presented a contribution entitled, "Spontaneous (Non-tubercular) Pneumothorax, with a Report of Cases and a Review of the Literature to Date" (illustrated with lantern slides).

This paper was discussed by Drs. Dock, Fussell, Barker, and Riesman. Dr. Smith closed the discussion.

Drs. J. H. Means and L. H. Newburgh presented, by invitation, a contribution entitled, "Observations with Krogh's Method of Blood Flow in Human Subjects," which was discussed by Dr. Hunt.

Dr. Edward C. Kendall demonstrated by lantern slides the effects of the "Iodine-containing Compound Occurring in the Thyroid."

This paper was discussed by Drs. Barker and Christian, and the discussion was closed by Dr. Kendall.

Dr. Thomas B. Futcher presented a communication on "Aleukemic Lymphadenosis," which was discussed by Dr. H. G. Wells.

Dr. J. C. Bloodgood, by invitation, presented a communication entitled, "The Condition of Patients after Partial or Complete Resection of the Colon."

This paper was discussed by Drs. W. B. Cannon, Meltzer, and Jacobi, and the discussion was closed by Dr. Bloodgood.

Drs. Thomas R. Boggs and M. C. Pincoffs presented a paper entitled "An Unusual Type of Pulmonary Mycosis."

Dr. Wm. Charles White presented a paper on "The Fate of Fats in the Blood Stream," which was not discussed.

Dr. Bailey K. Ashford presented a contribution entitled, "Studies in Moniliasis of the Digestive Tract in Porto Rico."

Dr. Edward J. Wood presented a contribution on "The Occurrence of Sprue in the United States."

The three preceding papers were discussed by Drs. J. H. Pratt, Thomas Ordway, and the discussion was closed by Dr. Ashford.

President Meltzer suggested the preparation of an index to cover the entire series of TRANSACTIONS for the past thirty years, and upon motion of Dr. Adams the Recorder was requested to prepare an index for the thirty volumes.

Upon motion of Dr. Dock the thanks of the Association were extended to President Meltzer for a highly interesting program and his services as presiding officer over a most successful meeting.

A vote of thanks was also extended to the Manager of the Hotel Raleigh for the very satisfactory accommodation for the meeting.

Adjourned at 1.15 P.M.

GEORGE M. KOBER,
Secretary.

The following papers were read by title:

"The Anatomical and Histological Expression of Increased Resistance toward Tuberculosis in Vaccinated Cattle," by Theobald B. Smith.

"Neurology Today and Thirty Years Ago," by Charles L. Dana.

"Present Status of the Specific Treatment of Epidemic Meningitis," by Simon Flexner.

"The Mechanism of Anaphylaxis and Anaphylatoxin Production," by F. C. Novy.

"Studies in the Pathology of Pituitary Dystrophy," by Aldred S. Warthin.

"Is there a Clinical Picture of Suppurative Nephritis?" by Richard C. Cabot.

"A Study of the Acidosis Occurring in the Nutritional Diseases of Infancy," by John Howland and W. McKim Marriott.

"Intravenous Injection of Dextrose and Depancreatization," by I. S. Kleiner and S. J. Meltzer.

"Magnesium Treatment of Tetanus," by J. Auer and S. J. Meltzer.

"The Hygiene of Aviators," by Geo. M. Kober.

"On the Probable Toxic Effect from Prolonged Administration of Parathyroid Gland Extract," by Roger S. Morris.

"Three Cases of Spinal Hemorrhage, with a Brief Discussion of the Etiology," by Harlow Brooks.

"Summary of Studies in Cortical Decomplication, with Remarks on the Nature of Certain Irritative Lesions," by E. E. Southard.

"A Study of Nephritis, Influences of Infections, Occupation, etc.," by Philip King Brown.

"Chronic Interstitial Nephritis and the Arteriosclerotic Kidney," by Oskar Klotz.

"Occupational Injuries Due to Radium (Personal Experience), with Report of Cases," by Thomas Ordway.

"The Occurrence of a Chronic Streptococcic Bacteriemia before and during the Development of Signs of Endocarditis," by J. A. Oille, D. Graham, and H. K. Detweiler.

ADDRESS OF THE PRESIDENT

THE AIMS OF THE ASSOCIATION OF AMERICAN PHYSICIANS

By S. J. MELTZER, M.D., LL.D.
NEW YORK

The first duty which the President has to perform is a sad one. I have to record the losses of the Association by death in the course of the past year.

Samuel Claggett Chew, Baltimore, original member, and emeritus member since 1897, died March 22, at the age of seventy-seven.

Morris Longstreth, Philadelphia, another original member, died in Barcelona, Spain, September 19, at the age of sixty-eight.

George Livingston Peabody, New York, died October 30, at the age of sixty-four. Dr. Peabody was an original member, served as secretary of the Association for one year and as a member of the Council for several years. He became an emeritus member in 1911.

Washington Emil Fischel, St. Louis, died September 15, at the age of sixty-four. He was elected to membership of the Association in 1895.

It is not only customary, but it is by order of the constitution, that the president opens the first session of the annual meeting by an address. As several other presidents before me, I shall use the words of the first president of the Association as a starting-point for my own remarks. President Delafield said: "We want an association in which there will be no medical politics and no medical ethics; an association in which no one will care who are the officers."

I shall deal first with the last-mentioned remark. We still do not care who the officers are. It is the prerogative and duty of the incumbent of the office of the presidency to express his views on subjects which concern the welfare of the Association. Now, I wish to say that in my opinion the members of the Association should care more than they do, who are the officers, and especially who shall be their president. In the course of our existence the constitution was so amended as to invest the president with autocratic powers, while his election gradually became, by mere custom, entirely undemocratic. I presume that not many of you know the exact procedure. The five councillors fill each year the vacancy in their ranks. The oldest councillor becomes vice-president and then president. While the recommendations of the council are formally submitted to your vote, I am not aware that they were ever voted down. In my opinion this oligarchic form of government harbors a danger. It may readily happen that the progressive majority of the members will be continually governed by intrenched regressive elements. I do not mean to imply that we are actually confronted with such a situation; I merely wish to call your attention to the possibilities which such an anomalous situation may have in store for you. I do not wish to offer any remedial suggestions; these must come from the members.

Having served as an officer of the Association for the last seven years, I am in a position to make the agreeable statement that medical politics and medical ethics still play practically no role in the procedure of election to membership in the Association. It holds true, in general, that each year of the numerous candidates the best men are elected to fill the vacancies. But I wish to state warningly that we are not entirely free from danger. I am not afraid that we shall ever elect to membership one who was convicted for a criminal act. But avoidance of coming in collision with the criminal code, or even a strict compliance with the ethical code of the American Medical Association, are not unrefutable evidences of high-mindedness. Commercial success in practice of medicine, social standing and social relations, manipulated publicity, the familiar principle of "one hand washes the other," and evils of a similar character are the pernicious elements which may endanger

the high standard of our Association. I speak not merely from theory. As president, I am entitled to express the wish that the Association should comprise not only the most-gifted, most-learned, and best-known physicians of the land, but should consist at the same time of high-minded, clean-handed men with a tinge of idealism. I appeal to you that in proposing candidates and electing them to membership the moral standard of the candidate should be one of the primary objects of consideration.

The reference of the first president to politics and ethics and the historical remarks of another president reveal the cause or, rather, one of the causes for the creation of this Association. It was chiefly the unsatisfactory conditions which prevailed at that time in the American Medical Association that caused medical men of a higher type to form new national associations. A generation has passed since the birth of this Association. The change in the standard of American medicine which took place in this comparatively short span of time is marvelous indeed. Was our Association an important factor in this progress? I believe that one of our presidents claimed it indeed. But justice compels me to state publicly that the credit for this achievement must be given chiefly to the great national democratic body, the American Medical Association. Since its reorganization, since the scientific part has been divorced from the politics of the Association, the character of the scientific proceedings changed completely. The purely medical work of nearly all the sections is now carried on generally by the scientifically productive, progressive, medical element of the whole country, who generally participate but little in the political activities of the organization. Furthermore, the new policies adopted by the reorganized association undoubtedly exerted a most beneficial influence upon the development of medicine in this country. I need only mention the work of the Council of Medical Education and of the Council of Pharmacy and Chemistry. The aims and the success of the last-named exerted even an international beneficent influence upon medical therapeutics. Not the least of the merits of the regenerated American Medical Association is the high standard which its journal is maintaining; it is undoubtedly now one of the best medical journals in the world. In this laudable work of the new

American Medical Association some of our members have taken an active part. But our Association as a body can not claim credit for the progress which was made in medical affairs of this country during the period of its existence; it was not brought about by any efficient designs or policies of this Association. If the Association of American Physicians exerted an elevating influence upon American medicine, it did so by its mere existence. When it was founded, a generation ago, the effort was made to incorporate in it the best medical men who could then be found in the country. Since then, year by year, an effort was made to admit only those who were the best of the available material at each period. With the introduction of the institution of associate membership a remedy was acquired to correct mistakes.

From the start our Association formed a constituent part of the body known as the Triennial Congress of American Physicians and Surgeons. Like the other constituent societies, for instance, the surgical or the ophthalmological, our Association represents a certain special part of the medical practice: it represents internal medicine. This Association, however, has one advantage over all of them. All practical medical subjects presuppose the knowledge of the pure medical sciences, for instance, physiology, pathology, bacteriology, pharmacology, or hygiene. But only the Association of American Physicians has the advantage of counting among its members investigators of these various sciences. I say, it has the advantage; there are some among us who may not consider it as an unmixed blessing.

Delafield, in the first presidential address, spoke of an association of physicians and pathologists. Osler, ten years later, added bacteriologists. We now have among our members also physiologists, pharmacologists, and investigators in the fields of hygiene and preventive medicine. Permit me to define my own position as to the aim and the composition of the membership of this Association. I entirely agree with the sentiment that the object of this Association is, and should be, clinical medicine in both of its aspects, the scientific and the practical. Purely physiological or chemical communications which have only a remote bearing upon medicine do not belong before this forum. Neither should medical scientists

whose work and interest are at a great distance from clinical medicine be elected to membership of this Association. But let me say this to you. For thirty odd years I have been engaged in a more or less active way in the scientific as well as in the practical side of medicine. It is my profound conviction that clinical medicine has a great future before it, but that the real success will come only from a close association of clinical medicine with the medical sciences.

The object of our Association is to increase our knowledge of the intricacies of medicine, to learn from one another the new things we have unraveled and to instruct one another in the art of advancing our knowledge. That object will be best attained when the men studying the sciences of medicine and the men studying and handling diseases will come together and have a chance to be stimulated and instructed by one another. Of course, both parties must be openminded, must be anxious to learn, and must have a deep interest in medicine and a full grasp of what it really means. Diseases are experiments which Nature makes on men and beasts. A mind trained in observing properly natural phenomena and studying critically experimental results is best prepared to interpret Nature's experiments, to grasp Nature's method in correcting physiological aberrations, and to try courageously to improve upon these methods and to discover or invent new ones. The best physician of the future will be the brainy man who spent many years in studying the methods employed in acquiring knowledge in the pure medical sciences and then in applying all his mental energies to a broad study of diseases. The field of the clinician is not confined to diagnosis and therapy alone, as was stated in one of the presidential addresses by a leading clinician. Great physicians were often also great original investigators. By diagnosis and therapy alone we would, for instance, have had no knowledge of Bright's, of Graves', or of Addison's disease; we would not have known of myxedema or acromegaly. In fact, a good deal of our knowledge of the significance of the ductless glands and internal secretion was established by clinical observations, and at first even against violent opposition of some classical physiologists. An instance, illustrating the value of coöperation between clinical men and men in the medical sciences,

is the discovery of the blood-pressure-raising principle of adrenin by Oliver and Schäffer. It was the physician Oliver who first noticed, by insufficient methods, that the administration of extracts of adrenals seemed to increase the blood-pressure. By obtaining the coöperation of the physiologist Schäffer, the subject was investigated by proper physiological methods and the discovery of adrenin, which attained such great importance, was safely established.

I therefore say again that it is of great advantage to our Association to have among its members investigators in the various fields of the medical sciences. Clinical medicine and medical sciences must be brought closely together and work in harmony; that will assure a steady progress of the science and practice of medicine. This union is what distinguishes our Association from other societies, and which gives it the right of continual existence.

Some older members complain that the papers presented at the meetings are getting above their heads. While this may be a fact, it can not be made the basis of a complaint. The papers of the program of an annual meeting reflect in general the character of the medical studies which prevail at that period. The science of medicine is progressing. Do these members wish that our science should stop progressing as soon as they, for one reason or another, can not follow it? The very same members who make this complaint were progressive at some time or another, otherwise they would not have become members of this Association. Their work at their time was probably above the head of those who remained then behind them.

If the character of the papers on our program reflects the nature of the problems which occupied the minds of our members in the past year, the number of these papers show their intense scientific activity. A long program awaits you and me. I shall have to be strict in enforcing the time limit of the speakers. I have the goodwill to be impartial, and shall therefore cut short my own remarks.

THE ANATOMICAL AND HISTOLOGICAL EXPRESSION OF INCREASED RESISTANCE TO TUBERCULOSIS IN CATTLE

FOLLOWING THE INTRAVENOUS INJECTION OF HUMAN AND ATTENUATED BOVINE TUBERCLE BACILLI[1]

By THEOBALD SMITH, M.D.
BOSTON

The following study is in effect a by-product of a series of experiments made from 1906 to 1911 to determine how far resistance to tuberculosis could be increased in cattle by preliminary injections of living tubercle bacilli of human and attenuated bovine type. This mode of vaccination, known as the von Behring method, has been repeatedly discussed by various investigators, and I shall not enter here into details concerning it. The results of our work have been published, but no description has been given of the form taken by the heightened resistance which is undoubtedly produced.[7] [8] Its anatomical expression has certain bearings upon the much-discussed question of phthisiogenesis in man, hence it has seemed worth while to give some details.

The calves included in the experiment (except No. 13) received two intravenous doses of human tubercle bacilli, a period of about two months intervening. A test inoculation with virulent bovine tubercle bacilli was made about two and one-half to three months after the second vaccination. At the time of this last test injection, untreated control calves were given the same injection. These all died of acute disseminated miliary tuberculosis within fifteen to twenty-eight days. The lungs in all cases were most severely involved. In addition to the countless tubercles there was a peculiar

[1] The plates are not reproduced here. They can be found in The Journal of Medical Research, 1915, xxxii, 455–469.

consolidation of the dependent lobes due to exudation of fibrin, immigration of endothelial elements into the alveoli, desquamation of alveolar cells, and marked injection of the capillary network. A considerable percentage of the vaccinated calves lived through this test inoculation and were in good condition about six months later when they were killed and autopsied.

The following table includes those cases which are more directly concerned in the present study. In it the most general data necessary to an understanding of what follows are given.

CALVES TREATED WITH HUMAN OR ATTENTUATED BOVINE TUBERCLE BACILLI AND TESTED WITH VIRULENT BOVINE BACILLI

Calf No.	Weight.	Date of first vaccination.	Culture used.	Date of second vaccination.	Date of test inoculation.	
12* . . . (control)	284	Dec. 8, 1906	Bovine IX (heated)	Feb. 7,1907	May 3, 1907	Killed May 22, 1907 (very ill)
35* . . . (control)	161	Dec. 7, 1906	Bovine IX (heated)	Apr. 19, 1907	June 28, 1907	Killed July 19, 1907 (very ill)
13	136	Dec. 12, 1906	Bovine I	Feb. 12, 1907	May 3, 1907	Killed Nov. 11, 1907
14	139	Dec. 12, 1906	HumanXXIV	Feb. 12, 1907	May 3, 1907	Killed Aug. 15, 1907 (light dyspnea)
30	240	Feb. 7, 1907	Bovovaccine	Apr. 19, 1907	June 28, 1907	Killed Nov. 4, 1907
37	219	Dec. 12, 1906	Human XIV	Apr. 19, 1907	June 28, 1907	Killed Nov. 1, 1907
146 . . .	227	Dec. 8, 1906	Human XII	Feb. 7, 1907	May 3, 1907	Killed Nov. 5, 1907
175 . . .	232	Dec. 8, 1906	Human VI	Feb. 7, 1907	May 3, 1907	Killed Nov. 8, 1907

* These calves may be regarded as controls, since the treatment had no effect whatever as compared with a number of bona fide controls not here tabulated.[7 8]

It was noted at the autopsies of the vaccinated cases that in the lung tissue there were variable numbers of subpleural lobules in a state of collapse. Usually but one lobule was involved in any given situation.

They suggested at first lesions due to aspiration of foreign bodies such as the writer observed many years ago in a case in which one tuberculous retropharyngeal lymph node was so enlarged that swallowing became difficult and aspiration of bits of fine hay, etc., into the trachea could not be avoided. These particles were found plugging the bronchioles of numerous collapsed lobules. In the animals here considered there was no such foreign-body element discoverable. Besides the red-flesh color characterizing collapse, some affected lobules had a yellowish gelatinous appearance indicating processes more advanced than simple atelectasis.

Sections made through material preserved in Zenker's fluid showed a variety of interesting changes. Unfortunately, the material had not been reserved for serial sections since the significance of the lesions was not understood at the time. The process in any one focus could not be traced from bronchiole to terminal alveoli as was done, for instance, by Abrikosoff[1] with human material. A considerable number of sections from a number of foci from five different animals made it possible, however, to construct fairly consistent pictures.

The dominant pathological process was a peribronchial cell infiltration with destruction of the overlying mucosa, ingrowth into and plugging of the lumen of the air-tube resulting in collapse of the parenchyma supplied by it. The presence of territories of collapse involving one or several lobules is very uncommon in spontaneous bovine tuberculosis. Of the many autopsies seen by the writer only a few presented such areas. Recently a number of fresh cases have been examined but none found with foci of collapse associated with tuberculous tissue.

The actual tuberculous lesions were insignificant and only suggested to the naked eye by the presence of collapsed lobules. They were in most cases limited to the lymph spaces around the bronchioles. The resulting quite broad peribronchial sheath of lymphoid cells with rare endothelial elements did not extend to the accompanying artery and vein (Plate II). These were found intact. The movement of the new cell growth was in all cases through the wall of the air-tube toward the lumen. As the mass grew in size the wall of the bronchiole bulged inward and gradually narrowed the lumen. Finally, only a very narrow lunar cleft remained (Plate II). At this stage, or even earlier, the epithelium had disappeared and the underlying structures of the wall were no longer recognizable. The mass projecting into the bronchiole presented an irregular jagged outline in cross-section. The tendency to proliferation was not exhausted at this step, but the invading cell mass continued to push its way into and along the lumen for some distance (Plate II, Fig. 4; Plate III, Fig. 6).

The collapse of the lobule supplied by the air-tube followed and the alveoli were to be sooner or later invaded and filled with the

advancing growth, its débris, or by aspiration. In the calves supplying this material the process had gone no further, but a case was found later which completes the picture. This last stage is a complete softening of the lobule and its contents. The lobule becomes a mere sac for the soft, cheesy mass, which, when discharged, leaves a small cavity behind.

The cell proliferation and cell accumulation differed markedly from that present in spontaneous tuberculosis of the lung tissue. Instead of the endothelioid cell groups which dominate the spontaneous lesions there were present lymphoid or granulation cells which sheathe the air-tube (Plate III, Fig. 5; Plate IV, Fig. 9). Endothelioid and giant cells were rare and not found in every section examined. Sometimes a rather large, atypical giant cell was found among large areas of lymphoid cells (Plate IV, Fig. 8).

In Case No. 13 the peribronchial cell masses were most like nodular collections of lymphoid tissue (Plate II, Fig. 3). No epithelioid or giant cells except a few containing carbon pigment were present. The new tissue was made up of small round cells, among which there were scattering large nuclei with very little chromatin, belonging to the adenoid network of cells such as we are accustomed to see in lymphoid tissue. In those cases in which the proliferative energy caused a destruction of the wall of the small bronchus and an ingrowth, the intrabronchial plug was made up of cells of the lymphoid and endothelial type commingled (Plate III). In some instances the cells showed signs of necrosis; in others, they were still of normal appearance. Polymorphonuclear cells penetrated the intrabronchial plug in different places. This intrabronchial mass was thus wholly different from the loose aggregation of cells of one kind, usually polymorphonuclear, which are encountered in ordinary bronchopneumonias and which are being pushed up and outward from the respiratory territories.

Lesions of the lungs due to the injection of bovine tubercle bacilli were not in all cases restricted to a peribronchial location. In some lungs, scattering tubercles were found in the parenchyma, evidently a result of the multiplication of bacilli in the capillary network. These were made up of a cluster of rather large atypical epithelioid cells enclosed in a small sheath of round cells. The

presence of these tubercles is not to be wondered at when we bear in mind the difficulty encountered in making homogeneous suspensions of cultures which are wholly free from clumps of bacilli. Such lesions were fairly proportional to the clinical picture. Those surviving animals which had a certain degree of fever and which did not increase in weight as rapidly as others, had the most "hematogenic" tubercles independent of the peribronchial localizations.

When these lesions are compared with those of the controls, differences are found from whatever angle they are viewed. In the controls, the parenchyma of the lungs was permeated with immense numbers of tubercles having their seat in the capillary network (Plate I, Fig. 2). In the vaccinated, the number of tubercles found in this situation was very small. Again, the tubercles of control animals were built up of the characteristic endothelial elements. The lesions of the treated animals were, as described, markedly atypical. An endeavor to put together the facts gathered from these cases and to formulate some theory tentatively accounting for them, leads us to the following statement:

In the control animals a large number of the tubercle bacilli injected into the jugular vein are held back in the capillaries of the lung where their presence leads to the formation of tubercles. These grow rapidly and through mechanical and toxic influences lead to the peculiar symmetrical pneumonic consolidation already referred to. In the treated animals the tubercle bacilli are held back equally and even more than in the untreated, but they are suppressed and destroyed, leaving the parenchyma nearly free. A few surviving bacilli after reaching the pulmonary capillaries are carried into the lymph vessels and are deposited in the peribronchial lymph channels. Here after a period of latency or repression they begin to multiply, forming the peribronchial sheath of granulation tissue which bursts into the lumen of the bronchiole and leads to collapse and subsequent tubercular liquefaction of the lobule. According to this theory the acquired immunity leads to a suppression more or less complete of the eruption of tubercles in the bloodvessels, but permits it to a certain degree after a time in the lymphatic system.

In young calves, to be used for the production of vaccine lymph,

the writer has not infrequently found a portion or even the whole of one of the smaller cephalic (anterior) lobes, in a more or less advanced stage of bronchopneumonia. In such cases a peribronchial cell infiltration is absent. The small air-tubes, and the alveoli in certain areas, are filled with masses of polymorphonuclear leukocytes. The mucosa itself is relatively intact. In one case, however, the bronchopneumonia was associated with or had grafted on it tuberculosis which showed itself in peribronchial cell masses growing into and occluding the lumen of bronchioles up to 3 millimeter in diameter. Whether in this case the tuberculosis was modified and retarded by the associated pneumonia so as to assume the type described, is a question not to be answered by this single case.

In most of the cases contributing material to this investigation there were evidences of activity of the injected bovine bacilli elsewhere in the body. This was restricted and evidently self-limited in the internal organs but not in such organs as the udder. In two cases udder tuberculosis occurred, although this organ was in only a partially developed state (Plate IV, Figs. 7 and 8). The type of lesion here agreed closely with that in the lungs. There was the same very active lymphoid-cell infiltration around the ducts and between the acini. Only occasionally a giant cell was encountered. The wall of the ducts was broken through and the growth pushed its way into and along the lumen as a cylindrical mass. In short, the tissue reaction was in lung and udder precisely the same.

As stated above, spontaneous tuberculosis of the lungs in cattle rarely presents collapsed lobules associated with the specific lesions. Nevertheless peribronchial tuberculosis followed by invasion and obliteration of the bronchiole is not uncommon. These apparently contradictory facts are easily harmonized. The lungs of tuberculous cattle usually present roundish, more or less uniformly caseous foci, often very large (Plate I, Fig. 1). These foci are evidently so uniform because the process is so rapid. The diffusion of tubercle bacilli probably takes place with such speed in all directions that all structures and tissues are equally involved. In the vaccinated cases the process is drawn out. Certain territories

such as the lung parenchyma are primarily immune and only secondarily overwhelmed when the disease descends the lumen of the bronchus after partial or complete collapse has been established. Owing to this chronicity we are enabled to distinguish the steps which follow each other so slowly.

In the liver of cattle and swine Joest and Ziegler[4] have described a process very similar to the one in our vaccinated cattle. Tubercular foci develop in the interlobular connective tissue. Thence they break through the wall of the bile duct into the lumen. In this way the bile is infected. An interesting question arises here in view of the fact that tuberculosis of the liver is usually secondary to earlier primary lesions. It may be asked whether the lesions described by Joest and Ziegler are due to a heightened state of resistance following the primary lesion elsewhere in the body or whether they occur as well when the liver lesions themselves are primary. In view of the conditions found in our vaccinated cattle as contrasted with the spontaneous disease this question is justifiable.

The change in the character of the tissue reaction due to vaccination is of more than passing importance. It has a practical bearing in so far as it emphasizes the warning so frequently expressed by pathologists that the anatomical and histological criteria of specific infectious diseases are not absolute. Various accessory factors and conditions may enter to modify the typical processes. These will become more accurately determined by the further development of experimental methods in infectious diseases and the study of unlooked-for and aberrant results following certain experiments. Two such cases were reported by the writer[9] with illustrations in 1911. The injection of tubercle bacilli of human type into cattle led to a marked stimulation of the growth of lymphoid cells around animal parasites. This reaction is not produced by either alone. Evidently a coöperation between the tubercle bacilli and the body substances or secretions of the parasite is necessary. The result is a lymphoma-like tumor, in the centre of which the parasite is embedded.

There is no tentative explanation to account for the change in the type of cell reaction due to partial immunization. In the

spontaneous tuberculosis of cattle, as well as in the disease induced in untreated animals by bovine bacilli, there is a predominance of endothelial elements, altered and changed into the abnormal epithelioid and giant cells in the tuberculous focus (Plate I). In our animals this gives way to granulation tissue the more the greater the acquired resistance. The most exuberant active growth, such as is found penetrating into bronchioles and continuing as plugs there, appears to be made up of endothelial and lymphoid cells intermingled. It may be that the immune substances brought out by vaccination and accumulated in the blood have deprived the bacilli of that which reacts and stimulates the phagocytic elements. What remains may be the factor which reacts upon the lymphoid elements. There is reason to assume from facts observed by the writer, but not here recorded, that as soon as the immune substance has disappeared the cell reaction reverts to the usual type.

The foregoing facts and interpretations are of importance quite apart from the practical question of the feasibility of immunization toward tuberculosis. This has been discussed in earlier papers and here we wish to call attention to any bearing they may have upon an explanation of the genesis of pulmonary tuberculosis in man. Since we have learned to recognize infection with bovine tubercle bacilli in the human body, the questions surrounding the beginnings of the lesion in pulmonary tuberculosis or phthisis have gained in interest and importance, and new ones have been added. There still remains the question why the initial lesions are localized in the upper lobes. The question as to the source of the infection, whether hematogenic or aërogenic, has been regarded as still open. In recent years advocates of the view that all infection is by way of the digestive tract, have taken the ground that the pulmonary lesion is largely secondary to invasion *via* the intestinal mucosa. This view and the doctrine promulgated by von Behring that most, if not all, pulmonary tuberculosis results from infection in infancy, remaining latent or quiescent until adolescence, have much in common. Lastly, the overwhelming percentage of cases of phthisis in which only the human type of bacilli is found has led to the doctrine of the transformation of the bovine into the human type of tubercle bacillus on its way from the digestive tract to the lungs.

The experimental approach to these problems is clouded by the fact that the virus used is usually attenuated as a result of selective growth on artificial culture media. It does not therefore represent the virus transmitted by nature. It is usually introduced into experimental animals in too large amounts, whereas spontaneous tuberculosis is incited by relatively few bacilli. The virus is, as a rule, not adapted to the species under experimentation. These objections, excluding the last, hold for the present investigation, and interpretations therefore must be cautiously made. Of the huge literature which has grown up around these problems only a few publications need be mentioned here.

Abrikosoff[1] studied the earliest recognizable changes in human pulmonary tuberculosis, making use of serial sections in tracing the location, extent, and movement of the lesion. In seven among four hundred and fifty-three autopsies the lesions began as a tubercular peribronchitis and bronchitis with subsequent aspiration into the terminal alveoli. Abrikosoff regards the lesions as the result of inhalation. Hematogenic tubercles, according to him, may have a variety of structures, one of them simulating the lesion of aërogenic infection. The author concludes that pulmonary tuberculosis starts as a peribronchitis of the intralobular bronchus, leads to dilatation, and continues centripetally and centrifugally as a lymphangitis tuberculosa peribronchialis. Neoplastic tissue may grow into the bronchus and caseate. He divides the process into a first act comprising caseous bronchitis and peribronchitis of the intralobular bronchus and its nearest branches, and a second act during which caseous masses are aspirated to produce pneumonic foci. The vessels are occasionally attacked leading to lymphangitis tuberculosa perivascularis and endovasculitis tuberculosa.

It will be noted that Abrikosoff states very clearly just what was found in the vaccinated bovine cases, with the exception that the bloodvessels in our cases were not involved. The bovine lesions were also slower in developing, without caseation, whereas in even the very early human lesions encountered Abrikosoff found caseation well along. The bovine cases suggest by analogy that in man the tubercle bacilli enter the alveoli from the air, and are carried thence into the roots of the bronchial lymphatics. Their movement

toward the lymph nodes being arrested, the peribronchial lesion is the result.

This leads us to a second important problem in human tuberculosis, the beginnings in the apical lobes of the lungs. Of recent attempts to explain this localization with the aid of animal experiments, Bacmeister's[2] should be mentioned here. Basing himself on the doctrine developed more than fifty years ago by W. A. Freund and taken up more recently by Hart and others, that pressure of the first rib due to anomalies of the first thoracic ring is responsible for the development of tuberculosis in the upper lobes, Bacmeister caused young rabbits to grow into a wire ring which was to produce compression very gradually and thereby narrow the chest aperture. Using a human type of tubercle bacilli he found after intravenous injection into "compressed" rabbits only typical tubercles, no peribronchial growth. When, however, he injected bacilli into the subcutis of rabbits which had been wearing the wire ring for six weeks he obtained the following results:

"In the first place, the peribronchial tissue is attacked, but in a few places the granulation tissue breaks through the wall of the bronchial tube. At such places the epithelium has disappeared or is permeated with lymphocytes. Genuine interstitial tubercles are nowhere to be found."

Lesions as described were also obtained by him when rabbits were exposed to a spray of tubercle bacilli, stenosis begun four weeks later, and the animals killed after another period of eight weeks. Bacmeister's thesis that all those moments lead to a localization and multiplication of tubercle bacilli in the apices, which interfere with the flow of lymph or produce stasis, seems to be borne out by his experiments. It is furthermore supported by the subpleural localization in our cases where the pressure of the ribs is most effective in locally interfering with the lymph current. It should be borne in mind that although every part of the lung tissue of our cases was flooded with bacilli, as shown by the condition of the lungs in the controls, yet only a small number of lesions resulted.

Bacmeister's results have been analyzed and repeated by Iwasaki,[3] who comes to different conclusions. He found Bacmeister's method

of inducing compression with a wire ring unreliable and, in his own experiments, he narrowed the thoracic aperture of the rabbits to be inoculated by resection of one of the first ribs. No results confirmatory of Bacmeister's theory were obtained. It should be stated, however, that Iwasaki's experiments are not sufficiently numerous to warrant definite conclusions. Fully one-half or more were made with bovine bacilli, which we know will develop in all parts of the rabbit's lung more or less uniformly. Those rabbits which were treated with human bacilli did not live long enough to permit a possible retrogression of tubercles in the main or caudal lobes and a full development of the lesions in the apical lobes. In making these criticisms I do not wish to convey the impression that I consider Bacmeister's experiments in any sense conclusive. They simply indicate that lesions similar to those described in the lungs of vaccinated cattle occur in rabbits following the injection of the human type of bacilli.

The lesions described by Abrikosoff, Bacmeister, and the writer lead eventually to cavities in the lungs. The production of such cavities among animals has interested a number of pathologists, since they are only rarely encountered. As far back as 1894 Prudden[5] found that the intratracheal injection of cultures of tubercle bacilli in rabbits followed by the intratracheal injection of streptococci, resulted in cavity formation. The cultures used were most probably of the human type, which within a period of six months have not led, in the writer's experience, to cavity-formation by themselves. Römer[6] encountered cavity formation very rarely and in such guinea-pigs which had been subcutaneously inoculated with tubercle bacilli of low virulence and which lived one to one and one-half years thereafter. This condition could, however, be produced more frequently by injecting into chronically tuberculous guinea-pigs a massive dose of tubercle bacilli. Other writers, among them Neufeld, Weber, and Titze refer to the production of cavities in goats, previously treated with human or avian bacilli, as a result of a test dose of bovine bacilli.

Cavity formation is, in general, a sign of resistance and in animals a sign of increased resistance usually due to some form of preventive inoculation or vaccination. It is associated with prolonged, chronic

types of tuberculosis and is probably in most, if not all cases, the result of peribronchial tuberculosis followed by invasion of the bronchiole, collapse, and tubercular infiltration of the associated respiratory territory. In the cases referred to, nothing was stated by the authors concerning the character of the lesions leading to cavity formation.

Conclusions. 1. The intravenous injection of tubercle bacilli of bovine type into calves, following preliminary injections of bacilli of human or attenuated bovine type, causes a heightened resistance which manifests itself by a shifting of the lesions from the parenchyma of the lungs, *i. e.*, the alveolar walls, to the bronchioles serving lobules or portions thereof. The affected lobules are subpleural.

2. The disease is chronic and progressive to a certain degree at least. It develops as a peribronchial inflammation in which lymphoid or round cells predominate. This may break through the wall of the bronchus, fill the lumen, cause collapse, aspiration of ingrowing cell masses with tubercle bacilli, and subsequent caseation of the collapsed territory.

3. Veins and arteries in the immediate neighborhood of affected bronchioles are not invaded.

4. The beginning of tuberculous changes in the wall of the minute bronchi is not in itself proof that the bacilli are air-borne, nor does it prove that inhaled bacilli have penetrated directly the mucosa of the minute bronchi. Localization depends very materially upon states of resistance of the host, or, what is equivalent, on the degree of virulence of the tubercle bacilli.

5. The type of cell reaction is the same in the udder as in the lungs.

6. Endothelioid and giant cells seem to be much more numerous in those cases whose acquired resistance is lowest.

7. The development of tuberculosis in the apical lobes in man is best accounted for by the less active aeration and less active lymph current. Rib pressure may contribute toward fixing the bacilli. Bacilli, deposited either from the air or the blood in other lobes, are either destroyed or promptly carried by the lymph current to the lymph nodes where they are gradually destroyed. The pheno-

menon of phthisis in man is strong evidence that the human being possesses a relatively high degree of resistance to the tubercle bacillus. This inference from comparative pathology has been abundantly proved in the past by autopsy records.

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3. Iwasaki. Deutsche Ztschr. f. Chirurgie, 1914, cxxx, 504.
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OBSERVATIONS ON CARDIAC DYSPNEA

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The work of Haldane and its subsequent development by Winterstein and Hasselbach indicated that under normal conditions the respiration is regulated by the acidity of the blood. This demonstration of the nature of the normal stimulus forms the starting-point for much of the recent investigation into the nature and cause of dyspnea in heart disease. The attempt has been made to determine whether in this pathological condition there is any quantitative or qualitative change in the stimulus to respiration. Lewis[1] and his associates have stated that in dealing with cardiac dyspnea it is essential to recognize two distinct groups of clinical cases, and this opinion has found support in other investigations. The mechanism by which dyspnea is produced apparently differs in some degree, according to whether the case is one of pure cardiac disease, or whether there is simultaneous involvement of the kidneys.

The patients with pure cardiac disease are in the main young persons with chronic valvular lesions. Orthopnea is present and cyanosis may be a more or less prominent feature. Dyspnea is frequently of high grade when the case is first admitted to hospital but does not usually persist. It is rather characteristic that although orthopnea may continue, and the slightest exertion suffice to cause breathlessness, these patients quickly regain their compensation so that when at rest and sitting in an erect position they are quite comfortable. Lewis found no evidence of an acidosis in this group of cases and he refers the dyspnea wholly to an inadequate supply

[1] Lewis, Ryffel, Wolf Cotton, and Barcroft, Heart, 1913, v. 45.

of oxygen. Studies of the alveolar air, however, have shown that during the acute stage, with severe dyspnea, there may be a well-marked diminution of the carbon dioxide tension. The acidosis which this implies is transient, and as the circulation readjusts itself the alveolar air returns to its normal composition. In other patients, even during the period of dyspnea, the carbon dioxide tension does not vary from its normal value. Thus the dyspnea of pure cardiac disease may or may not be associated with the development of an acidosis. In either case the cause of the dyspnea is probably the same and depends on insufficient circulation. With the failing heart and slowing of the circulation carbon dioxide may accumulate in the respiratory centre and stimulate it to increased ventilation. If the heart becomes very weak, so that the amount of oxygen reaching the tissues is greatly reduced, there will be incomplete combustion of the substances formed during cellular metabolism, and acids will appear in the blood. These, in their turn, will augment the stimulus to respiration, and by increased ventilation of the lungs, the carbon dioxide will be reduced. Since the kidneys are normal the excretion of acid will go on rapidly, and as soon as the circulation has readjusted itself, the excess of non-volatile acids will have been excreted, and the alveolar air will return to normal.

In the second group of dyspneic patients the element of acidosis, as it is a more permanent feature, plays a more significant part. Clinically these are usually elderly persons, often with the pallor of arterial or renal disease, and with comparatively little cyanosis. Orthopnea is present, and particularly characteristic are sudden attacks of severe dyspnea, occurring especially at night. The respiration is rather shallow, irregular, and frequently of the Cheyne-Stokes type. The patients are often dull or sleepy, and they may doze off during the periods of apnea, arousing suddenly with great distress during the periods of dyspnea. The urine is that of a chronic nephritis, and the blood-pressure is usually well above normal. Renal function determinations, as indicated by the phthalein test and the non-protein nitrogen in the blood, indicates that these are generally cases with extensive degeneration of the kidneys. The condition is most often a permanent one, lasting days, weeks, or even months before death, but sometimes there are transient or

fairly prolonged intervals with a return to comparative comfort and health. In general the condition indicates serious organic disease and the prognosis is grave. Analysis of the alveolar air in this clinical condition shows that it is quite generally associated with a fall in the carbon dioxide tension. This decrease is not great, however, and the values are most frequently between 35 and 30 mm., though they sometimes reach as low as 25 mm. In almost all the cases in which the symptom-complex has been clear cut, and the acidosis evident, the functional tests have shown that the kidneys were decidedly inefficient. It is thus probably correct to assume that the acidosis is due to an accumulation depending on incomplete excretion, and is in large part of renal origin. Since, however, these patients usually have a weak heart as well as diseased kidneys, there are two possible causes for an acidosis, and the relative importance of each can only be determined by careful study of the individual case.

It is extremely difficult to decide exactly how significant the element of acidosis is in producing the dyspnea of cardiorenal disease. In diabetes, the same grade of acidosis, as indicated by the alveolar air, produces no gross changes in the respiration. Only when a much greater depression of the alveolar carbon dioxide has taken place, is the breathing noticeably affected, and a wholly different type of respiration results. The deep, regular respiration of diabetic acidosis is totally unlike the shallow, rapid, irregular periodic respiration of cardiorenal disease. If, then, the dyspnea of cardiorenal disease depends on acidosis alone, it must be that there are other factors which modify the way in which the organism reacts. On the other hand, merely because the acidosis is not very great, one should not conclude that it is of no significance. Some observations in which the respiratory function has been tested by using carbon dioxide in the inspired air as a means of increasing the stimulus to respiration throw light on this point.

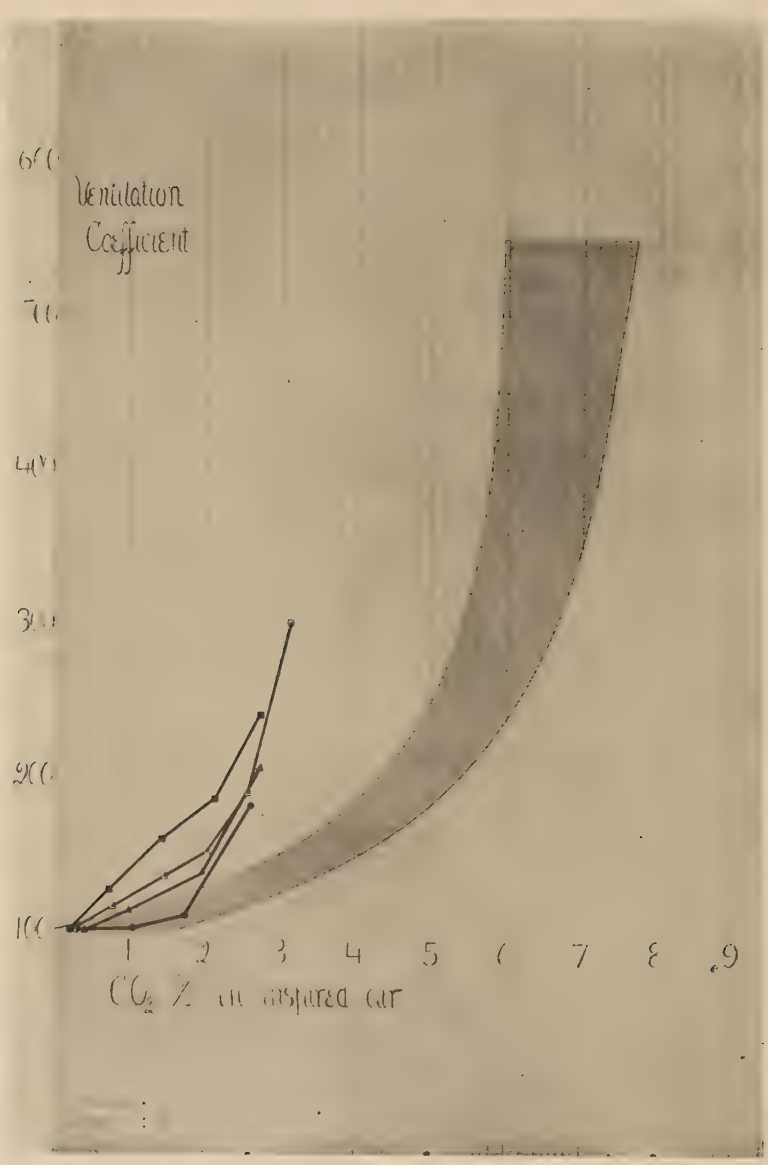
Subjects have been allowed to breathe through valves attached to a so-called "closed-circuit" apparatus. The expired air passes through two large tanks, and is subsequently rebreathed, so that the inspired air has a continually increasing content of carbon dioxide. A volumetric spirometer is connected into the circuit, and

its movements are recorded on the smoked paper of a kymograph. By means of a scale the depth of each single respiration and the total ventilation per minute can be measured. At regular intervals during the experiment samples of the inspired air are taken for analysis. Thus the volume of the ventilation, and the increase over its initial, normal value, can be compared directly with the percentage of carbon dioxide in the inspired air.

It has been found that normal individuals react in a fairly constant manner to the added stimulus. Thus when the carbon dioxid reaches a concentration of between approximately 4.3 and 5.4 per cent., the subjects are breathing so deeply that their initial ventilation has been doubled. In a series of normal subjects varying in type from a large, well-trained, athletic young man, to a frail girl of fourteen, the percentage increase of ventilation caused by a given amount of carbon dioxide was so nearly constant that a curve could be drawn which will include the normal variation. (See chart.) A very much greater difference exists in the maximum concentration of carbon dioxide which the various subjects could breathe without too great discomfort, and in the maximum ventilation they were capable of.

The same test has been applied to patients with cardiac and cardiorenal disease. It has been found that if the patients are compensated while they are at rest in bed, and if they have no evidence of acidosis as shown by the alveolar air, the response is almost precisely that of normal individuals. It takes the same amount of carbon dioxide to double the ventilation in the cardiac patients as it does in the normals. The fact that the patients with cardiac lesions were not more easily affected by the carbon dioxide in the inspired air is quite striking, for the cases studied were all such that a very slight amount of exercise would induce marked dyspnea.

The results were quite different with the decompensated cases, both cardiac and cardiorenal, in whom the analysis of the alveolar air showed the presence of an acidosis. These patients were much more sensitive to the carbon dioxide in the inspired air, and in some instances the total ventilation was doubled when the the carbon dioxide concentration had only reached between 2 and 3 per cent. (See chart.) Dyspnea was very easily produced, and they were not



Ordinates show the percentage increase in pulmonary ventilation; abscissæ the concentration of carbon dioxide in the inspired air. The shaded curve represents the reaction of normal individuals (the ventilation is doubled when the inspired air contains 4.25 to 5.40 per cent. CO_2). The black lines show the results with patients having acidosis (the ventilation is doubled when the inspired air contains only 2.25 to 2.75 per cent. CO_2).

able to breath air containing nearly as high a percentage of carbon dioxide as could either the cardiac cases without acidosis or the normal individuals. The increase in sensitiveness to carbon dioxide bears a very direct relation to the degree of acidosis, as is shown by observations on a single patient made on two occasions. On the first day his total ventilation was nearly doubled when the inspired air contained only 2.62 per cent. carbon dioxide, and the discomfort was so great that the experiment had to be stopped. The alveolar carbon dioxide tension was at this time 34.5 millimeters. Some days later he was given sodium bicarbonate. After receiving 95 grams, the urine became alkaline, and the alveolar carbon dioxide rose to 47.3 mm. tension. Another respiration experiment was tried and the response was found to be perfectly normal. The ventilation did not become doubled until the concentration of carbon dioxide in the inspired air had reached 4.66 per cent., and with this amount neither the dyspnea nor the distress were particularly noteworthy. The explanation of this peculiar sensitiveness of patients with acidosis to an increase of the carbon dioxide of the inspired air is found in the unusual conditions in the blood. On account of its content of the salts of weak acids, sodium bicarbonate, monosodium phosphate and disodium phosphate, as well as owing to the large amounts of protein which it contains, normal blood is able to take up a great quantity of acid without any noticeable shift in its true reaction being produced. But beyond a certain point the mechanism fails, and the addition of even small amounts of acid changes the reaction. This is apparently the state of affairs in the cases with acidosis. The blood has already taken up all the acid it can without having its reaction affected, and the addition of any more, as in breathing the air containing carbon dioxide, suffices to cause a shift in the blood reaction and to increase the pulmonary ventilation. The same result would undoubtedly be brought about if the carbon dioxide was produced in the body, as by muscular exercise. The amount of muscular work which would suffice to produce dyspnea would be much less than normal. Some recent observations by Christiansen, Douglas, and Haldane[1] are

[1] Jour. of Physiol., xlviii, 244.

wholly in accord with this explanation. They found that the increase of lactic acid in the blood after severe exercise "led to an enormous temporary alteration in the absorption curve" of carbon dioxide, and a marked reduction in the amount of carbon dioxide which the blood would take up at a given tension.

Thus, while the degree of acidosis which is present in cardiorenal disease is usually insufficient to cause the changes in respiration which one is accustomed to associate with acidosis, or to explain the dyspnea completely, it is, nevertheless, undoubtedly an important element. It renders the organism unusually sensitive to any added production of acid, and would, in all probability, accentuate the effect on the respiration which might be caused by an inefficient heart.

IMPORTANT CONTRIBUTIONS TO CLINICAL MEDICINE DURING THE PAST THIRTY YEARS FROM THE STUDY OF HUMAN BLOOD-PRESSURE

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INTRODUCTION

Although Vierordt's crude attempts to measure the compressibility of the pulse by the attachment of weights to a sphygmograph were made many years before, the clinical study of blood-pressure really dates from the publication by von Basch, in 1881, of work done with his first sphygmomanometer. When this Association first met, thirty years ago, interest in the new method was confined to von Basch and his immediate pupils, and neither the transactions of this society nor the standard text-books on practice of the day make the slightest reference to the method or its results. In the sixth edition of Flint's *Practice of Medicine*, published in 1886, in the preparation of which Dr. William H. Welch assisted, and which represented the best clinical knowledge of that time, one finds statements such as these:

"A well-recognized form of cardiac hypertrophy is that which is secondary to certain forms of chronic Bright's disease, particularly to the small, granular kidneys. The explanation of this is not thoroughly understood. It will be referred to under the head of Bright's disease. Suffice it to say here that it is probably due to some resistance to the blood current through the small vessels;" and "As already stated, simple hypertrophy of the left ventricle of the heart may have a causative relation to cerebral hemorrhage by increasing arterial tension." In describing the clinical history

of apoplexy he says: "The pulse is usually diminished in frequency, full and hard, the artery striking against the finger like a metal rod."

These quotations show the clear recognition, by the unaided senses of the clinician, of the existence and associations of high blood-pressure, but no material advance in its detection or in the study of the problems presented by it since the days of Richard Bright, half a century before.

In 1891 an important paper on Bright's disease was presented before this association by Dr. Francis Delafield.[1] In it he speaks frequently of contraction of the arteries and of the disturbance of the circulation, to which he attributes the cerebral symptoms and dropsy of nephritis and for which he advocates drugs which dilate the arteries. The same year a discussion of the relations between arterial disease and visceral changes was led by Drs. Peabody[2] and Councilman,[3] and participated in by such distinguished clinicians as Drs. Ord and Gairdner, with casual allusions to increased arterial tension and spasm of the arteries, but no reference whatsoever to the existence of any clinical knowledge of blood-pressure.

In 1899, Dr. Stengel read a paper upon the immediate and remote effects of athletics upon the heart and circulation, without making any mention of blood-pressure, and in the discussion which followed Dr. Meigs made this remarkable statement:

"The doctrines that were generally accepted twenty years ago in regard to Bright's disease and the hypertrophy of the heart so commonly associated with it have fallen almost entirely into discredit. We used to be told that kidney disease caused increased resistance within the arteries, and this threw more work upon the heart, which in answer underwent hypertrophy and grew strong. Little is heard of this any more, and Bright's disease is less and less frequently used as a diagnostic term."

[1] Delafield, Francis. On the Diseases of the Kidneys Popularly Called Bright's Disease. Trans. Assn. Amer. Phys., 1891, vi, 124–154.

[2] Peabody, George L. Relations Between Arterial Disease and Visceral Changes. Trans. Assn. Amer. Phys., 1891, vi, 154–178.

[3] Councilman, William T. On the Relations between Arterial Disease and Tissue Changes. Ibid., 179–192.

The first paper that dealt with blood-pressure specifically was the important presentation at the twelfth meeting, in 1897, by Abel and Crawford, of the isolation of chemically pure epinephrin.[1] This was, however, experimental work.

The first report of observations on human blood-pressuré was made in 1903 by Dr. Richard C. Cabot, as part of a paper describing "Studies on the Action of Alcohol in Disease, Especially upon the Circulation." This was a careful clinical study of a therapeutic problem in 58 cases, the Riva-Rocci sphygmomanometer and the original Oliver hemodynamometer being the instruments employed.

At the meeting in 1904 another paper by Dr. Cabot[2] dealt altogether with blood-pressure measurements, and two by Dr. Stengel[3] contained studies on arterial pressure. One of these[4] was in collaboration with the late Dr. W. B. Stanton, who played an important part in securing the adoption of the sphygmomanometer by the American practitioner as part of his armamentarium.

From the year 1906, when the association so kindly endured my maiden presentation on hypertension, to the present time, no meeting has been without several papers on blood-pressure problems, clinical or experimental, and for the past seven years all have shown that clinical blood-pressure measurements have become a permanent part of the routine examination of the circulatory system.

In 1886 the literature of human arterial pressure, so far as I have been able to collect it, comprised twelve titles. It is not wholly without regret that I find that my personal bibliographic references in this field for the past ten years amount to more than one thousand titles. From this mass of accumulated knowledge of the behavior of the blood-pressure in health and disease, what real gain has there been to clinical medicine?

[1] Abel, J. J., and Crawford, A. C. On the Blood-Pressure Raising Constituent of the Suprarenal Capsule. Trans. Assn. Amer. Phys., 1897, xii, 461–480.

[2] Cabot, R. C. Measurements of Blood-pressure in Fevers Before, During and After the Administration of Strychnin. Trans. Assn. Amer. Phys., 1904, xix, 22–23.

[3] Stengel, A. Clinical Studies in Arteriosclerosis. Trans. Assn. Amer. Phys., 1904, xix, 512–518.

[4] Stengel, A., and Stanton, W. B. The Heart and Circulation in Pregnancy and the Puerperium. Ibid., 520–553.

I. A METHOD OF OBSERVATION

A method of sufficient accuracy and sufficient ease of application to satisfy the requirements of medical practice is now available. The contributions toward the elaboration of our present instruments and the methods of their application for the determination of the systolic and the diastolic pressures, and the critical studies to which they have been subjected, are among the most important that I have to record.

To von Basch we owe the first real sphygmomanometer and the first observations of human blood-pressure which have any value. Potain[1] in 1899 made the first important modification by introducing air in place of water as the medium for the transmission of the pressure. In 1896 Riva-Rocci,[2] and in 1897 Leonard Hill,[3] independently devised the method of circular compression by which the main inaccuracies in the application of the sphygmomanometer were overcome. In 1901 von Recklinghausen[4] demonstrated that the chief error which remained was dependent upon too narrow a compressing armlet, and introduced the wide cuff which has since become universal. In 1905 Korotkow[5] published his method of auscultatory determination, which has supplanted all other methods for the clinical measurement of the diastolic arterial pressure.

At the present day accurate sphygmomanometers of varying types, to suit the requirements of hospital, consulting room and family practice, are obtainable in every country. An accurate sphygmomanometer consists of a tested manometer, a compressing bag 12 cm. in width for the arm, an inflator fitted with a needle-valve for the slow release of pressure, and connecting tubing. Many types of instruments now discarded have contributed to the

[1] Potain. Arch. de phys. norm. et path., 1889, i, 556.

[2] Riva-Rocci, S. Un nuovo sfigmomanometro. Gazz. med. di Torino, 1896, xlvii, 981, 1001.

[3] Hill, Leonard, and Barnard, Harold. A Simple and Compact Form of Sphygmometer or Arterial-pressure Gauge Devised for Clinical Use. Brit. Med. Jour., 1897, ii, 904.

[4] v. Recklinghausen, H. Ueber Blutdruckmessung beim Menschen. Arch. f. exper. Pathol. u. Pharmakol., 1901, lxvi, 78.

[5] Korotkow. Berichte der kaiserlichen Militärärztlichen Akademie. Petersburg, 1905, xii, 395.

production of the present form and have been of great service in the critical study of methods—especially the early instruments of Marey and Mosso, by which diastolic pressures were first approximately studied, the graphic instrument of Erlanger, the various

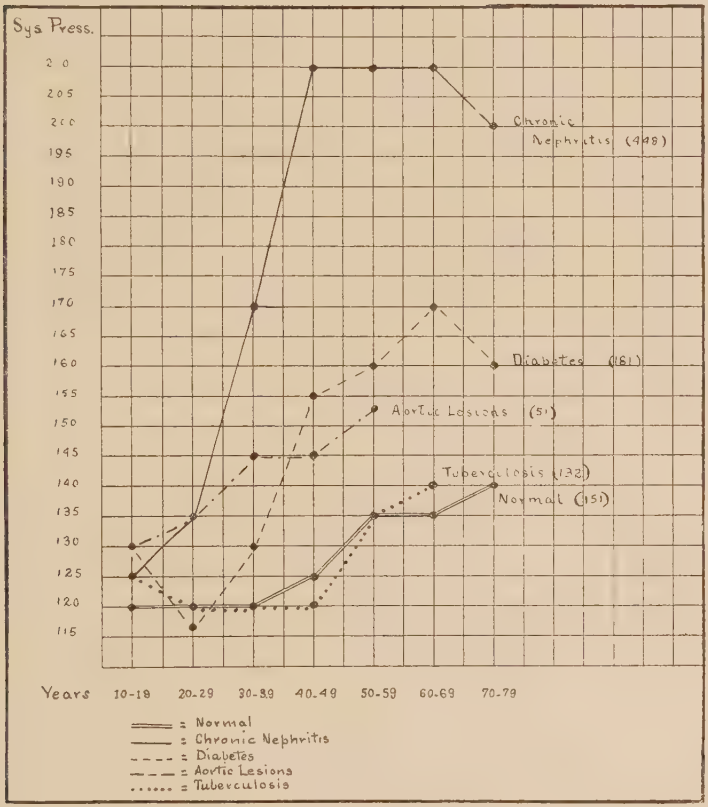

CHART 1.—Median systolic blood-pressures, arranged by age periods. Personal observations. (Figures in brackets at right of curves indicate total number of individuals observed in each group.)

portable instruments of George Oliver, and the instruments of Hill and Barnard and of Gibson. In this country H. W. Cook first introduced a portable form of the Riva-Rocci apparatus. The tonometer of Gärtner was undoubtedly a factor in promoting clinical studies of blood-pressure, though its usefulness has passed.

As a matter of fact, the auscultatory index for the diastolic pressure has made every instrument employing circular compression of the upper arm available for any clinical use.[1]

From among the many studies, critical and experimental, which have contributed to the perfection of the method, to single out those of conspicuous importance in the development of clinical sphygmomanometry is difficult, and to mention them all quite impossible. In this country the work of Erlanger, of Cook and Briggs, and of Stanton is especially important; in England that of Leonard Hill and his various collaborators, of George Oliver, and more recently of MacWilliam and his co-workers. Gallavardin in France, and in Germany, Hensen and Gumprecht were among the pioneers, and von Recklinghausen and Ottfried Müller have rendered conspicuous service. The monographs dealing with the methods and results of blood-pressure study have also been valuable in promoting a widespread use of the instrument.[2]

The only significant factor of error which is still inherent in the bloodless measurement of human arterial pressure is due to the resistance of the arterial wall itself. This was first emphasized by Russell,[3] and was so overemphasized as to call forth experimental investigations, which have now determined its importance.[4]

[1] For Full Discussion and Description of Methods see Norris: Blood-Pressure, its Clinical Applications, Philadelphia, 1914, p. 63, et seq. Also MacWilliam and Melvin: Estimation of Diastolic Blood-pressure, Heart, 1914, v, 153–196.

[2] The following monographs are worthy of record:

v. Basch, S.: Die Herzkrankheiten bei Arteriosclerose. Berlin, 1901.

Potain, C.: La pression artérielle de l'homme à l'état normal et pathologique. Paris, 1902.

Oliver, G. Studies in Blood-pressure, Physiological and Clinical. London, 1902.

Janeway, T. C. The Clinical Study of Blood-pressure. New York, 1904.

Pal, J. Gefässkrisen. Leipzig, 1905.

Müller, O. Der arterielle Blutdruck und seine Messung beim Menschen. Ergeb. d. inn. Med. u. Kinderheilk., 1908, ii, 367–417.

Gallavardin, L. La tension artérielle en clinique. Paris, 1910.

Horner, A. Der Blutdruck des Menschen. Leipzig, 1913.

Norris, G. W. Blood-pressure: Its Clinical Applications. Philadelphia, 1914.

A full literature will be found in these monographs.

[3] Russell, W. Arterial Hypertonus, Sclerosis and Blood-pressure. Edinb. and Lond., 1908, p. 87.

[4] Since the study presented by Park and myself before this association in 1910 (An Experimental Study of the Resistance to Compression of the Arterial Wall. Arch. Int. Med., 1910, vi, 586), the following important publications have appeared:

Gallavardin, L. and Haour, J. Baisse systolique de la tension artérielle au moment de la mensuration. Arch. d. mal. du cœur, 1912, v, 81.

MacWilliam, J. A. and Kesson, J. E. The Estimation of Systolic Blood-pressure

It is altogether probable that in all normal persons and in the vast majority of patients the resistance offered by the arterial wall to external compression is negligible, but in a few patients with arterial disease such resistance is clearly the cause for overestimation by clinical instruments of the actual blood-pressure. As both Gallavardin and MacWilliam have shown, repeated compression of the artery in most of the cases abolishes the local tonus responsible for this error. It is also possible, as MacWilliam has demonstrated, and as I have found in my own work, to detect the cases in which this error is important by making both palpatory and auscultatory determinations of the systolic pressure, these patients showing a striking divergence between the two indices. With these exceptions, and the necessary avoidance of excitement and other environmental influences on blood-pressure, it is now possible for the clinician to determine with a high degree of accuracy both the maximum or systolic, and the minimum or diastolic, pressure. Thiry years ago only the most approximate measurements of the systolic pressure were possible.

II. CONTRIBUTIONS TO DIAGNOSIS

Clinical blood-pressure studies have been of greatest value as an aid in diagnosis. Even the earliest and crudest confirmed and greatly extended the older clinical observations on the significance of the high tension pulse in the diagnosis of chronic renal disease. All subsequent studies have emphasized hypertension as a cardinal symptom of chronic Bright's disease—a symptom now more easily detected than any other manifestation of the disease. One has but to turn to Flint's *Practice*, to see how completely the sphygmomanometer has revolutionized the diagnosis of this affection. On page 889 the following statement begins the

in Man with Special Reference to the Influence of the Arterial Wall. Heart, 1913, iv, 279.

MacWilliam, J. A., Kesson, J. E. and Melvin, S. The Conduction of the Pulse Wave and its Relation to the Estimation of Systolic Blood-pressure. Ibid., 393.

Hill, L. and Flack, M. The Effect of Lability (Resilience) of the Arterial Wall on the Blood-pressure and Pulse Curves. Proc. Roy. Soc. Lond., 1913, lxxxvi, s. B., 365.

Wells, S. R. and Hill, L. The Influence of the Resilience of the Arterial Wall on the Blood-pressure and on the Pulse Curve. Ibid., 180.

discussion of the diagnosis of chronic Bright's disease: "The diagnosis of chronic as of acute Bright's disease is to be based on the evidence afforded by examination of the urine." Certainly no medical teacher at the present time would regard the urinary findings as the first evidence of this type of renal disease, though recognizing their great importance. The curves from my own blood-pressure observations, shown in Charts 1 and 2, strikingly illustrate the diagnostic importance of hypertension in chronic renal disease.

In 1886 the detection of albumin and casts was relatively easy and objective, and the discovery of high blood-pressure in many cases difficult and to a large extent dependent upon the special skill of the examiner. At the present day the detection of high blood-pressure is absolutely simple and wholly objective, and we have learned how misleading it is to infer from the presence or absence of albumin and casts either the presence or absence of chronic Bright's disease.[1]

With increasing use of the sphygmomanometer all observers began to encounter patients with hypertension without the urinary evidences of nephritis and without renal symptoms. Such patients had previously been supposed to suffer from idiopathic hypertrophy of the heart. The opinion has gradually developed that a symptom-complex exists in which the symptom first in importance and in time of development is increased arterial pressure. Patients presenting this symptom-complex suffer, as a rule, from minor grades of myocardial insufficiency or from cerebral symptoms, or present an indefinite neurasthenic state. Evidences of renal insufficiency are conspicuously absent during the earlier stages. The condition has been given various names—latent *angiosclerosis* by von Basch, *presclerosis* by Huchard, *hyperpiesis* by Allbutt. I have preferred to call it *primary hypertensive cardiovascular disease*. It is often spoken of merely as *hypertension* or *essential hypertension*, and has recently been designated *benign essential hypertension* by Volhard and Fahr.[2] It has therefore neither a uniformly accepted

[1] Statistical data on this point will be found in my paper, A Clinical Study of Hypertensive Cardiovascular Disease. Arch. Int. Med., 1913, xii, 755. Also Trans. Assn. Amer. Phys., 1913, xxviii, 333.

[2] Volhard, F. and Fahr, Th. Die Brightsche Nierenkrankheit. Berlin, 1914.

name nor a universally accepted interpretation, but is everywhere recognized as one of the commonest types of circulatory disease. This recognition is due entirely to the sphygmomanometer.

Those who dislike terms which express a functional and not an anatomical diagnosis have included these cases either in the category

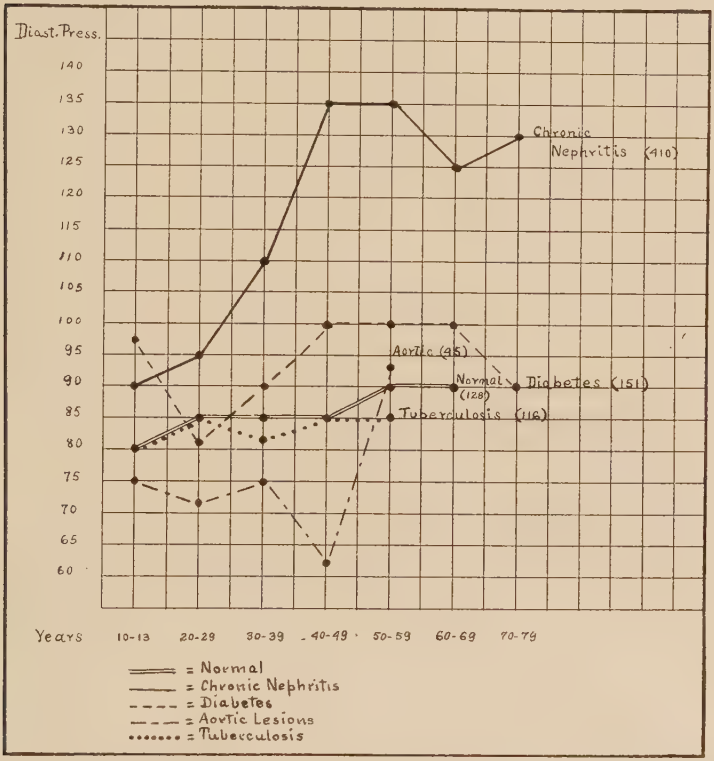

CHART 2.—Median diastolic blood-pressures, arranged by age periods. Personal observations. (Figures in brackets at right of curves indicate total number of individuals observed in each group.)

of chronic nephritis or of arteriosclerosis. The careful study of the blood-pressure in each of these conditions, however, does not warrant the view that the continued existence of the symptom hypertension is in itself sufficient ground for the diagnosis of one or the other of them in the sense in which the terms are ordinarily

used. I have already discussed this at length elsewhere.[1] Suffice it to say here that all observers agree that widespread sclerosis of the accessible peripheral arteries or of the aorta may exist with normal or low blood-pressure. Therefore hypertension is not a necessary sequence of ordinary arteriosclerosis. On the other hand, while the study by finer methods of the kidneys of such patients as die has shown that in almost all of them some changes in the smaller renal vessels and in the glomeruli can be made out,[2] nevertheless there is no parallelism whatever between the extent of the kidney lesions and the height of the blood-pressure. In the end-stages these patients may certainly exhibit the anatomical picture of the primary contracted kidney. In the early stages, however, as Jores has so clearly pointed out,[3] the kidney is only one of the organs implicated in the widespread disease of the arterioles, and may show but little change. To consider essential hypertension, therefore, wholly of renal origin is unwarrantable at the present time; and a functional designation may be wisely retained, unless the term "arteriolar sclerosis" can find acceptance.

The foregoing condition occurs frequently after middle life, but is peculiarly common in elderly diabetics (see Charts 1 and 2). On the other hand, it is clear from my own observations and those of Elliott,[4] that diabetes itself is without influence on the arterial pressure. Hypertension is therefore presumably an expression of the well-known tendency of diabetics of suitable age to develop arterial disease; or possibly in some cases arterial disease is the cause of the lesions responsible for the diabetes.

In the differential diagnosis of the type of existent renal disease blood-pressure observation plays a conspicuous part. Great stress has been laid upon this by Volhard and Fahr in their recent monograph.[5] Without going quite to the same length of schematic differentiation, it can be said that, in patients presenting the other

[1] Janeway, T. C. Nephritic Hypertension: Clinical and Experimental Studies. Amer. Jour. Med. Sci., 1913, cxlv, 625.

[2] Fischer, J. Ueber die Beziehungen zwischen anhaltender Blutdrucksteigerung und Nierenerkrankung. Deutsch. Arch. f. klin. Med., 1913, cix, 469.

[3] Jores, L. Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis. Virchows Arch., 1904, clxxviii, 367.

[4] Elliott, A. R. A Clinical Study of Blood-pressure Variations in Diabetes and Their Bearing on the Cardiac Complications. Jour. Amer. Med. Assn., 1907, xlix, 27.

[5] Volhard, F., and Fahr, Th. Die Brightsche Nierenkrankheit. Berlin, 1914.

evidences of kidney disease, increased blood-pressure always suggests either primary disease of the vessels or true diffuse nephritis. As I have seen hypertension develop during the early anuria of necrosis of the kidney from bichloride of mercury, however, I do not believe, as they do, that it can be considered as absolutely differentiating between the degenerative nephroses on the one hand and the inflammatory nephritides and vascular scleroses on the other. A persistently subnormal blood-pressure in a patient with renal symptoms is certainly the strongest evidence of amyloid kidney. In clinical acute Bright's disease hypertension regularly indicates a true diffuse nephritis or a severe renal insufficiency.

Of less diagnostic value, but still a real contribution to clinical medicine, has been the study of blood-pressure in increased intracranial tension. This has been thoroughly elucidated by animal experimentation. In the differential diagnosis of coma, hypertension always suggests cerebral hemorrhage acting in this way, or uremia associated with a preëxisting hypertensive nephritis.

Transient hypertension has been exhaustively studied by Pal.[1] Of the so-called vascular crises which we have learned to recognize, that accompanying puerperal eclampsia is the most important. Blood-pressure studies have strikingly confirmed the early observations of Vaquez[2] that a persistent hypertension after the delivery of the child points to eclampsia as probable. Similarly, hypertension has been shown to accompany lead colic and the gastric crises of tabes, and has some diagnostic value in cases of obscure abdominal pain. Exophthalmic goitre is associated with moderate elevation of blood-pressure in a large proportion of cases.

In the diagnosis of the other forms of circulatory disease, blood-pressure studies have yielded little of importance. Normal blood-pressure in a patient with myocardial insufficiency without valvular disease helps materially toward the diagnosis of primary disease of the myocardium. It is a striking fact, however, as Starling[3] and others have shown, that a moderate hypertension commonly

[1] Pal, J. Gefässkrisen. Leipzig, 1905.

[2] Vaquez and Nobécourt. De la pression artérielle dans l'éclampsie puerpérale. Bull. et mém. Soc. méd. d. hôp. de Paris, 1897, xiv, 117.

[3] Starling, H. J. Observations on the Arterial Blood-pressure in Heart Disease. Lancet, 1906, ii, 846.

accompanies myocardial insufficiency, the pressure falling as the circulation improves.

In the study of the valvular diseases of the heart, blood-pressure observation has proved valuable only in the diagnosis of aortic regurgitation. This is facilitated in two ways: first, by the demonstration of the increased pulse pressure in those cases which do not show a typical collapsing pulse (see Charts 1 and 2), and second, by the very interesting finding, first made by Hill and Flack,[1] that the systolic blood-pressure in the leg in aortic regurgitation is regularly higher than in the arm—sometimes to an astonishing extent. I am personally convinced of the diagnostic value of this discrepancy between arm and leg pressures, which does not seem to be found in other pathological conditions or in normal individuals when due precautions are taken.

As an aid to clinical diagnosis subnormal blood-pressure has been of relatively little value. While it commonly accompanies the infectious diseases and cachectic states, it is but one of many symptoms and the diagnosis does not depend upon its discovery. In the recognition of amyloid disease and of Addison's disease, however, a persistently low blood-pressure is of very real importance. In the detection of internal hemorrhage the discovery of a falling arterial pressure, and especially of a falling pulse pressure and pulse rate, as described by Wiggers,[2] may be significant. A fall in pressure during pleural aspiration has been shown by Capps and Lewis[3] to be an indication of reflex inhibition of the heart or vasomotor centre. The relation of low blood-pressure to surgical shock, while of great value to the surgeon, is beyond the limits of this paper.

[1] Hill, L. and Flack, M. The Accuracy of the Obliteration Method of Measuring Arterial Pressure in Man. Proc. Physiol. Soc., Lond., 1908–9, p. 48.

These observations have been confirmed by Hare (The Difference between Systolic Pressure in the Arm and in the Leg in Aortic Regurgitation. Trans. Assn. Amer. Phys., 1910, xxv, 91), by Hill and Rowlands (Systolic Blood-pressure in Cases of Aortic Regurgitation. Heart, 1912, iii, 219), by Rolleston (On the Systolic Blood-pressure in the Arm and Leg in Aortic Incompetence. Ibid., 1912, iv, 83) and by Murray (Systolic and Diastolic Blood-pressure in Aortic Regurgitation. British Med. Jour., 1914, 697).

[2] Wiggers, C. J. The Prognostic Significance of Pulse-pressure Changes during Hemorrhage. Arch. Int. Med., 1910, vi, 281.

[3] Capps, J. A. and Lewis, D. D. Blood-pressure Lowering Reflexes from Irrigation of the Chest in Emphysema. Trans. Assn. Amer. Phys., 1909, xxiii, 188.

The early investigators of blood-pressure, especially in France, beginning with Marfan,[1] believed low blood-pressure to be an important indication of tuberculosis. Norris[2] still states that tuberculosis is generally associated with hypotension. My own observations have convinced me that as a factor in the diagnosis of tuberculosis blood-pressure measurements have no real value. A glance at the curves in the accompanying charts (Charts 1 and 2) shows in striking fashion the essential correspondence of the curve of the normal and the curve of the tuberculous individuals, as observed in an office practice. Shalet,[3] who has examined about 1000 patients at the Otisville Sanatorium, has come to the same conclusion. It is of course unquestionable that in advanced and febrile tuberculosis a low blood-pressure exists and has the same significance as in other active infections.

Is there a state of constitutional or essential hypotension, as there is of essential hypertension, as has been held by Bishop and a few other observers?[4] At the present time I am not convinced of this, for I have personally observed systolic pressures which would ordinarily be considered subnormal—below 110 in men and 95 to 100 in women—existing over long periods of absolutely perfect health and physical activity. Low blood-pressure, in the cases to which the term "constitutional low blood-pressure" has been applied, is merely one symptom of lowered tone of the central nervous system—though possibly an important one to recognize.

For the final determination of the importance of slight deviations from the average blood-pressure in normal individuals a

[1] Marfan, B. J. A. De l'abaissement de la tension artérielle dans la phthisie pulmonaire. Compt. rend. Soc. de biol., Paris, 1891, iii, 346.

La tension artérielle dans la tuberculose pulmonaire chronique et son importance pour le pronostic. Rev. d. méd., 1907, xxvii, 1005.

[2] Norris, G. W. Blood-pressure; Its Clinical Applications. Philadelphia, 1914, p. 199.

[3] Shalet, L. Blood-pressure in Pulmonary Tuberculosis. New York State Jour. Med., 1914, xiv, 189.

[4] Bishop, L. F. Constitutional Low Arterial Tension in Children. Ann. Gynec. and Pediat., 1906, xix, 85. Also Jour. Amer. Med. Assn., 1906, xlvii, 1734. Constitutional Low Arterial Tension and its Relation to the Life of the Individual. New York Med. Jour., 1906, lxxxiii, 967.

Goodman, E. H. Some Cases of Hypotension Associated with a Definite Symptomatology. Amer. Jour. Med. Sci., 1914, cxlvii, 503.

Norris, G. W. Blood-pressure: Its Clinical Applications, Chap. VI. Essential Hypotension (Constitutional Low Arterial Pressure).

knowledge of the limits of normal variation is essential. Its attainment necessitates a vast number of observations and has therefore taken much longer than the acquisition of a knowledge of the more marked pathological changes in pressure. The real basis has been afforded by the introduction of the sphygmomanometer in life insurance examinations. Since the publication by Fisher[1] of the blood-pressure records of 19,339 accepted candidates for life insurance, all previous tabulations of average pressures in normal adults can be discarded as inadequate. Fisher's table follows:

Ages.	Number.	Average blood-pressure.
15–20	281	119.85
21–25	785	122.76
26–30	791	123.65
31–35	689	123.74
36–40	2,111	126.96
41–45	6,740	128.56
46–50	4,471	130.57
51–55	2,371	132.13
56–60	1,100	134.78
Totals	19,339	128.91

Dr. Fisher has written me personally that since this publication he has been informed of a record of 9000 readings by another company which did not vary one millimeter in the average of any age from those he has tabulated—making an average standard based upon the observation of over 28,000 healthy adults. However, for the decision that a particular blood-pressure reading is beyond the possible normal it is necessary to know not only the normal average but the limits of variation at any age. This must be so much a matter of opinion as to the health of the individual showing a debatable abnormal blood-pressure that there will always be a difference of opinion about it. I am inclined to revise my former opinion and to agree with Cook,[2] and Lauder Brunton before him, that over 135 mm. up to middle life, and 145 or 150 mm. thereafter, should be regarded as pathological hypertension if found on repeated examinations. For the lower limits of normal pressure in adults I should take 100 mm. in women and 105 to 110

[1] Fisher, J. W. The Diagnostic Value of the Sphygmomanometer in Examinations for Life Insurance. Jour. Amer. Med. Assn., 1914, lxiii, 1752.

[2] Cook, H. W. Blood-pressure in Prognosis. Med. Rec., 1911, lxxx, 959.

in men, though attaching less significance to occasional readings slightly below this.

The diastolic pressure is unquestionably of great importance, and in the determination of abnormally high or low blood-pressure should have equal consideration, but it is as yet so little used that a consideration of it would go beyond the scope of the present paper (see Chart 2).

The tabulation of my personal blood-pressure readings in persons without detectable disease, as shown in Charts 1 and 2, is interesting as showing how closely a comparatively small series of observations may follow the averages obtained in such a large series as Fisher's. Of course, the smaller the series the less smooth the curve, but the figures are strikingly similar.

All figures for the normal individual bring out clearly the definite tendency of the blood-pressure to increase with advancing years. The effect of age, however, is most strikingly seen in childhood, and within recent years a large number of important studies on blood-pressure in children has been published.[1] In this particular field of study the oscillatory method—which I believe gives erro-

[1] Durand-Viel, P. Des variations de la pression artérielle au cours de quelques maladies chez les enfants. Paris, 1903.

Stone, J. S. Report on Blood-pressure Determinations Made at the Boston Children's Hospital. Div. Surg., Harvard Med. School, 1903–4, i, Bull. No. ii, 18.

Trumpp, J. Blutdruckmessungen an gesunden und kranken Saüglingen. Jahrb. f. Kinderh., 1906, lxii, 43.

Gaujoux, E. Recherches sur la tension artérielle normale chez les enfants. Ann. de méd. et chir. inf., 1908, xii, 435.

Stowell, W. L. Blood-pressure in Children. Arch. Pediat., 1908, xxv, 88.

Kaupe, W. Der Blutdruck im Kindesalter. Monatsch. f. Kinderh., 1910, ix, 257.

Seiler, F. Praktische Bemerkungen über den Blutdruck und über Normalwerte des Blutdruckes im Kindesalter. Cor.-Bl. f. schweiz. Aerzte, 1910, xl, 433.

Wolfensohn-Kriss, P. Ueber den Blutdruck im Kindesalter. Arch. f. Kinderh. 1910, liii, 332.

Salle, V. Ueber Blutdruck im Kindesalter. Jahrb. f. Kinderh., 1911, lxxiii, 273.

Jarricot. Mesure de la tension artérielle chez les enfants et oscillométre de Pachon comme sphygmo-signal. Péd. prat., 1912, x, 392.

Koessler, L. L'oscillimétrie appliquée à l'étude de la tension artérielle chez les enfants. Paris, 1912, No. 144.

Balard, P. Le pouls et la tension artérielle de l'enfante et du nouveau-né. Gaz., des hôp., Paris, 1913, lxxxvi, 837.

Friberger, R. Ueber die Entwicklung von Puls und Blutdruck im späteren Kindesalter, Arch. f. Kinderh., 1913, lx, 331.

Katzenberger, A. Puls und Blutdruck bei gesunden Kinder. Kinderh., 1910, ix, 257.

Leitao, M. Pression artérielle chez l'enfant. Arch. d. méd. d. enf., 1913, xvi, 102.

Judson, C. F. and Nicholson, P. Blood-pressure in Normal Children. Amer. Jour. Dis. Children, 1914, xii, 257.

neous results in adults—has found a special application, because neither the palpatory nor the auditory index of blood-pressure can be readily used in very small children. The accompanying chart (Chart 3) from Koessler's article shows very clearly the rapid rise of pressure during the growth period of the child. In using it for absolute values, however, one must remember that the oscillometric method gives an overestimation of the systolic pressure. The majority of those who have studied this aspect of the question agree with Wolfensohn-Kriss, that the chief parallelism of the blood-pressure in childhood is with the increasing height and body weight rather than with age itself, and that the slightly lower pressure seen in girls and in women, when compared with males of the same ages, is related to the lesser height and weight rather than to sex itself.

An interesting study has been made by Wildt[1] of blood-pressure in the aged. He found the following average blood-pressures:

Ages.	Systolic.	Diastolic.
60–64	137	76
65–69	143	78
70–74	148	80
75–79	152	82
80–84	148	78
85–89	162	85
90–96	129	59

These averages represent readings on 250 individuals, without the exclusion of those who showed circulatory or other disease. The percentages showing marked hypertension in this group were as follows:

	Systolic pressures.	
Ages.	Over 150.	Over 200.
65–69	49 per cent.	3 per cent.
70–74	44 "	6 "
75–79	39 "	7 "
80–84	38 "	12 "
85–89	64 "	14 "

These pressures were quite regularly associated with chronic nephritis or arteriosclerosis. Hypotension he found only in tuberculosis and pneumonia, in six cases of contracted kidney and in

[1] Wildt, H. Ueber Blutdruck im Greisenalter. Zentralbl. f. Herzkrankh. u. Gefässkrankh., 1912, iv, 41.

individuals with weak hearts. There was a regular tendency for the amplitude or pulse pressure to increase, the diastolic pressure frequently being lower than in earlier life. It is interesting that in the four individuals above ninety the pressure was much lower than at the preceding age periods.

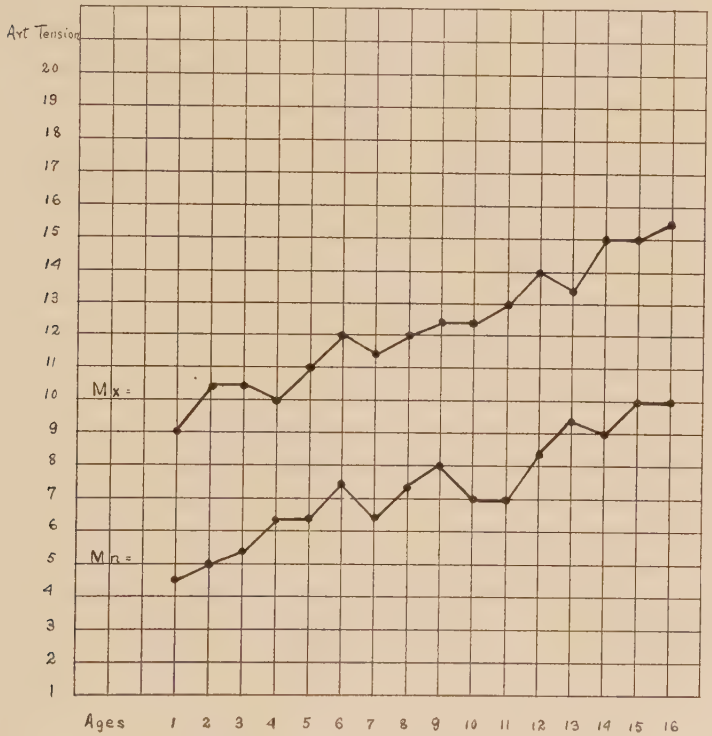

CHART 3.—Curve of pressures arranged by ages (boys), from "L'Oscillométrie appliquée à l'étude de la tension artérielle chez les enfants," L. Koessler, Paris, 1912, p. 65.

An important observation on blood-pressure in the normal adult male has been made by Chamberlain[1] in the Philippines, showing, from the examination of 992 American soldiers, that the average pressures in the tropics are lower than the normal averages for

[1] Chamberlain, W. P. A Study of the Systolic Blood-pressure and the Pulse Rate of Healthy Adult Males in the Philippines. Phil. Jour. Sci., 1911, vi, 467.

temperate climates and that the pressure was lower during the first three months of tropical residence than subsequently, and on the average about 3 to 5 mm. lower during the hottest season of the year. His table is as follows:

Ages.	Number.	Average blood-pressure.
18–20	36	115
20–25	469	114.3
25–30	286	115.9
30–35	109	116.7
35–40	58	120.5
Over 40	34	119.6

He failed to find any marked parallelism between blood-pressure and the height and weight of the individual. The mean pressure of Philippinos during the same age periods did not differ from that of Americans.

III. CONTRIBUTIONS TO PROGNOSIS

So far, the most important application of blood-pressure measurements to the solution of prognostic problems has been made by the life insurance companies. This is quite natural, since the entire business of life insurance is based upon scientific prognosis. Only recently, however, have actuaries attempted to make statistical studies of prognosis in disease, and the results of this application of statistics, on a scale sufficiently large to reduce the influence of individual error and variation to a negligible quantity, are of great importance to the medical profession. Physicians rarely have the opportunity to observe hypertensive patients until they develop symptoms, whereas the life insurance examiner has the opportunity to detect these conditions before any other evidence of deviation from the normal exists. During the years from 1907 to 1910, the company of which Dr. Fisher is medical director accepted 2661 applicants, with an average blood-pressure of 142.43, between the ages of forty and sixty, and their average mortality was practically the mortality of all of the insured. During the same period the company accepted 525 persons with an average pressure of 152.58, or only 10 mm. above the average of accepted risks. These persons showed a mortality 30 per cent. above the

general average of the company. They rejected 1970 applicants with an average pressure of 161.44 between the years 1907 and 1913, and, when followed up, these have shown a mortality more than double the average for the company—and this is probably below the facts, because of incomplete returns.

These figures are eloquent testimony to the value of the instrumental measurement of blood-pressure in the early recognition of what is frequently the sole evidence of a deviation from the normal in middle-aged persons. Fisher states that but little value is attached as yet to their observations of low pressure.

Apart from the general indication which hypertension gives of the eventual probability of the development of symptoms of myocardial insufficiency, renal insufficiency or cerebral vascular disease, the study of blood-pressure has not yet led to important gains in the ability to predict duration of life. In particular, it is clearly a mistake, as I have emphasized in a previous report before this association,[1] to assume that an individual with extreme hypertension will die sooner than one with a moderate elevation of blood-pressure. The blood-pressure reading is an additional factor to be combined by the physician with all the other symptoms and signs presented by the patient in arriving at that most difficult of practical judgments, a prognosis as to the duration of life. Rapidly falling blood-pressure is a frequent terminal symptom in hypertensive patients dying of uremia, and, as in apoplexy, is a very bad omen. I have also found a steady rise in pressure to be a serious feature in cases of chronic diffuse nephritis, usually indicating the development of severe renal insufficiency.

In the early days of blood-pressure study I, like most physicians interested in this field, hoped that it would furnish most important indications in acute infectious disease. That hope has been disappointed. I think that most of us must now agree with the conclusions of Kurt Weigert[2] from his extensive studies of the various acute infections, and which have been confirmed, for scarlet fever,

[1] Janeway, T. C. A Clinical Study of Hypertensive Cardiovascular Disease. Arch. Int. Med., 1913, xii, 755. Also Trans. Assn. Amer. Phys., 1913, xxviii, 333.

[2] Weigert, K. Ueber das Verhalten des arteriellen Blutdrucks bei den akuten Infektionskrankheiten. Samm. klin. Vortr., 1907, No. 459 (Inn. Med., Nr. 138), 65.

by Rolleston,[1] that the value of the blood-pressure measurement for prognosis in the acute infectious diseases is slight. It is an additional factor which is occasionally useful, as in typhoid patients with hemorrhage; but for the most part the simpler observations made by our predecessors in clinical medicine, of the facies, the tongue, the pulse, the heart sounds and the state of the nervous system make the prognosis equally well without a knowledge of the blood-pressure curve. That further observations may permit of greater refinement in this field is not to be denied.

In one disease—lobar pneumonia—so good an observer as Gibson[2] thought he had discovered a most important prognostic indication in the relation of blood-pressure and pulse rate, which has become known as Gibson's rule. The rule is that, when the blood-pressure, expressed in millimeters of mercury, falls below the pulse rate per minute, expressed in figures, the prognosis is unfavorable. But a recent critical study by Newburgh and Minot[3] has shown that the prognostic inferences based on Gibson's rule were oftener wrong than right in their 15 cases. They emphasize the fact that low systolic pressures are not "invariably of evil omen," and in this I heartily concur.

IV. CONTRIBUTIONS TO THERAPEUTICS

In the progress of practical medicine, advances in the diagnosis of disease have usually preceded advances in therapeutics, often by a very long period. In the treatment of diseases associated with high blood-pressure the ability to detect hypertension led at first to widespread abuse of vasodilators. Further study, however, clearly showed both the difficulty of permanently lowering the blood-pressure by drugs and the occasional harm produced in these patients by successful vasodilatation; and, as a result, the treatment of essential hypertension today is the treatment of the patient and not of the hypertension—safe-guarding treatment in

[1] Rolleston, J. D. Blood-pressure in Scarlet Fever. British Jour. Child. Dis., 1912, ix, 444.

[2] Gibson, G. A. Some Lessons from the Study of Arterial Pressure. Edinburgh Med. Jour., 1908, n. s., xxiii, 17.

[3] Newburgh, L. H., and Minot, G. R. The Blood-pressure in Pneumonia. Arch. Int. Med., 1914, xvi, 48.

the strictest sense—the endeavor is to avoid myocardial or renal insufficiency, or a vascular accident, and to limit the operation of known causes for hypertension.

The most remarkable claims for the therapeutic control of hypertension have been made by physicians employing the so-called "d'Arsonvalization," a special form of high frequency current. A critical study of this whole literature has been to me far from convincing. A vast majority of the publications have been by Moutier. He has used very inaccurate instruments for the measurement of blood-pressure. In his most important account of 50 cases treated,[2] in 43 the fall in pressure could have been explained by the well-known tendency for first readings to be higher than subsequent ones, and could be duplicated from my records of untreated cases. Of his remaining seven cases, in only five was there any reduction in pressure which could be considered at all permanent, and in not a single case was there any fore-period of observation to determine the spontaneous variations, which, in hypertensive patients, may assume considerable proportions.

A study of 266 cases of arteriosclerosis by Bühler[2] is on its face rather more convincing. The few patients in whom I have been able personally to control the effects of this treatment, unknown to the physician who was administering it, have shown no result whatever, although a marked effect was claimed by the electrotherapeutist. The whole subject, however, is deserving of scientific and objective investigation.[3]

Until the real mechanism by which high blood-pressure is produced shall be thoroughly understood, neither preventive nor curative treatment can be developed. The use of the sphygmomanometer has, however, contributed largely to the more careful study of these patients, and thus indirectly to their more intelligent treatment. It affords a means of gauging objectively the necessary dose of a vasodilator when one must be used—and incidentally

[1] Moutier, A. and Challamel, A. Sur 50 nouveaux cas d'hypertension artérielle permanente traités par la d'arsonvalization. Ann. d'électrobiol., 1904, vii, 657. Also Rev. d. mal de la nutrition, 1905, iii, 82.

[2] Bühler, A. Erfolge der Hochfrequenzströme bei Arteriosklerose. Med. Klin., 1914, x, 55.

[3] For Further Literature on Therapeutics in Hypertension see Norris: Blood-pressure: Its Clinical Application, Chap. xiii, p. 273.

has given proof of the inertness of many of the preparations of vasodilating drugs upon the market. Thus blood-pressure studies, from the standpoint of therapeutics, have been largely critical and negative.

They have been of great importance in respect to one drug, digitalis. That digitalis—a pharmacological action of which in the intact animal is to produce marked vasoconstriction—does not tend uniformly to raise the blood-pressure in hypertensive patients with myocardial insufficiency, or, if it does, improves the circulation at the same time, has been especially emphasized by Sahli,[1] and has gradually become common knowledge.[2] This is a matter of the first importance, because we have no substitute for the digitalis bodies in myocardial insufficiency.

Control by the sphygmomanometer of the so-called cardiac or circulatory stimulants has shown how misplaced has been the faith of physicians in such drugs as strychnine and caffein as a means of combating circulatory failure in acute infectious diseases or in surgical shock.[3] The various hydrotherapeutic procedures have been studied in the same way, and a large literature is growing up on the subject.

In the treatment of acute infectious disease I think we must still agree with Weigert[2] that knowledge of the blood-pressure does not help us, though this may be because of inadequate development of the methods for measuring the pulse pressure. It is possible that a very careful critical study of systolic, diastolic and pulse pressures may give the observation of the arterial pressure a greater importance in acute diseases than it possesses today.

[1] Sahli, H. Ueber Herzmittel und Vaso-motorenemittel. Kong. f. inn. Med. Verhandl., 1901, xix, 45.

[2] Martinet, A. Pressions artérielles et viscosité sanguine. Paris, 1912.

Lawrence, C. H. The Effect of Digitalis on the Blood-pressure and Pulse Pressure in the Presence of Cardiac Decompensation. Boston Med. and Surg. Jour., 1914, clxx, 37.

Janeway, T. C. The Comparative Value of Cardiac Remedies. Arch. Int. Med., 1914, xiii, 361.

[3] Newburgh, L. H. The Use of Strychnine and Caffein as Cardiovascular Stimulants in the Acute Infectious Diseases. Arch. Int. Med., 1915, xv, 458.

Crile, G. H. Blood-pressure in Surgery. Philadelphia, 1903.

V. CONTRIBUTIONS TOWARD A FUNCTIONAL PATHOLOGY OF THE CIRCULATION

In my opinion the clinical study of blood-pressure during the past thirty years has justified the time devoted to it, as much by its contribution to medical theory as by its contribution to medical practice. Prevention of disease must always depend upon a knowledge of causation and transmission, and its adequate treatment upon a complete understanding of the mode of production of the lesions and the symptoms which together constitute the phenomena of disease. The problem of the etiology of the chronic so-called degenerative diseases is one of the greatest awaiting solution at the present day, and the first approach to it must be from the standpoint of accurate clinical observation. Clinical medicine, not animal experimentation, determines and defines the problem.

The accurate measurement of the blood-pressure in patients with cardiovascular disease has afforded a mass of incontrovertible facts, which are essential for the attainment of a sound functional pathology of the circulatory system. Increased blood-pressure has been found to be the earliest and the most important functional disturbance in a very common type of circulatory disease. Its association with certain lesions of the arteries, in the kidneys and elsewhere, has been determined. Its development has been traced in other cases where obvious renal disease has preëxisted. In a considerable number of cases the evidence strongly suggests that the increased arterial pressure develops parallel with changes in the arteries rather than as their sequel. Many associations of temporarily high blood-pressure with intoxications and other abnormal conditions have been discovered. In addition, the effects of myocardial insufficiency, of acute infections, and of other complicating disturbances in lowering a persistent hypertension are being worked out in greater and greater detail. Accessory hypertensive influences are being similarly described with greater completeness. The problem of the cause of the hypertrophied heart in chronic Bright's disease engrossed the generation preceding ours. For us it has become the problem of the cause and the pathological physiology of permanent hypertension. This is more than a change

in emphasis. It means an accumulation of exact knowledge derived from clinical observation by a physiological method which has already enlarged our understanding of a pathological process, of which the lesion in the heart is an end result, and has brought the problem one step nearer solution.

In spite of the considerable advance in our knowledge of the modes of production of hypertension in animals and the remarkable discoveries concerning the action of the adrenals and other ductless glands, the problem of the causation of hypertension still awaits solution. The clinical observation of blood-pressure by family practitioners over a long period of years, now that the sphygmomanometer has become a routine instrument, may yet contribute data of importance toward this much desired end.

From a purely negative standpoint the discovery that myocardial insufficiency, as in valvular diseases of the heart, results in a great reduction in the arterial blood mass, but not in arterial blood-pressure, while at first sight disappointing to physicians seeking only aid in the immediate practical problems of medicine, is an important fact in circulatory pathology. It shows the presence of a compensatory vasomotor mechanism in cardiac disease. In states of supposed circulatory collapse in acute infectious disease the same disappointment has been met with. The sphygmomanometer has failed to reveal the expected extreme hypotension until the agonal period. But the sphygmomanometer has given us facts in place of inferences from crude methods. Similarly, graphic and electrical methods are refining the analysis of the cardiac rhythms. From these facts, when combined with like accurate observations by other physiological methods, there will yet be constructed a functional pathology of the circulation which will be the basis for the successful treatment of patients with circulatory disease.

STUDIES OF THE BLOOD FLOW BY THE METHOD OF KROGH AND LINDHARD *

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(By Invitation)

The all-important function of the heart is its ability to pump a sufficient amount of blood in a unit of time. All the properties of the myocardium subserve this function. Within the last decade we have learned much about some of these properties. We have, at the same time, been made aware of the very great difficulty of judging of the ability of the pump on the basis of such data. It is accordingly of the greatest importance to get direct information in regard to the volume of the circulation, or, as it is more commonly called, the blood flow.

Methods. Methods for studying the blood flow have been devised by various investigators, notably, Bornstein,[1] Krogh and Lindhard,[2] Zuntz[3] and his co-workers, Plesch,[4] and by Haldane[5] and his co-workers. We have selected the Krogh-Lindhard method as being most suitable for our purposes. The principle involved is, briefly, to determine the rate of absorption of nitrous oxide in the lungs. Since nitrous oxide is a readily soluble gas, yet one which forms no chemical combination with hemoglobin, it will go into solution at body temperature according to a definite coefficient. This coefficient has been determined by Siebeck.[6] This being true, if, after having breathed a mixture of air and nitrous oxide, the

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subject holds his breath for a certain length of time, and we then determine the percentage of nitrous oxide in the alveolar air at the beginning and the end of this period, together with the total amount of gas enclosed in the chest during the period of holding the breath, we can calculate how much blood must have passed through the lungs to remove the amount of nitrous oxide which has disappeared.

The factors which will be considered are the total blood flow per minute, the volume per beat and the coefficient of utilization of the oxygen carrying capacity of the blood.* The pulse rates are those taken just before the blood flow experiments.

The oxygen capacity of the blood of the various subjects was determined from their hemoglobin, Haldane[7] having shown that the oxygen capacity is directly proportional to the hemoglobin determined colorimetrically. A Hellige colorimeter which has been calibrated in terms of a normal blood, the oxygen capacity of which had been determined by the Barcroft differential blood gas apparatus was used for the hemoglobin determinations.

Experiments with the Krogh-Lindhard Method. Three subjects were studied by this method, two normal and one a case of double aortic and mitral disease, compensated. The oxygen capacities of these subjects were, L. H. N. normal, 173 c.c. per liter; J. H. M. normal, 193 c.c. per liter; C. L. cardiac, 173 c.c.

Experiments with the Normal Subjects. In Tables I and II will be found the resting values for L. H. N. and J. H. M. These experiments were all done with the subject lying flat on the back and after he had been in that position for at least a half hour.

The figures are very similar to those obtained by Krogh and Lindhard and show considerable variation in the blood flow during rest. The subject L. H. N. has a somewhat higher average blood flow and volume per beat than J. H. M., but a lower oxygen absorption, consequently the former's coefficient of utilization is also somewhat lower.

* The principles, calculations, and technique have been thoroughly discussed by Krogh and Lindhard. The figures for the blood flow appearing in the following tables are both the actual, and the so-called reduced values, of these authors.

The determinations of the oxygen absorption were made either directly before or after the blood flow experiments, by means of the Douglas respiration apparatus.

TABLE I.—SUBJECT, L. H. N.; RESTING EXPERIMENTS LYING FLAT ON BACK

Experiment No.	Date.	Values found in blood flow experiment.					Reduced values.					Ventilation of lungs liters per minute.
		Oxygen c.c. per minute.	Blood flow liters per minute.	Oxygen per liter of blood c.c.	Pulse.	Volume per beat c.c.	Oxygen c.c. per minute.	Blood flow liters per minute.	Co-efficient of utilization.	Pulse.	Volume per beat c.c.	
		a	b	$\frac{a}{b}=c$	d	$\frac{b}{d}=e$	A	$\frac{A}{a}b=B$	C	D	$\frac{B}{D}=E$	
39A	Dec. 28	418	7.59	55	89.5	84	248	4.50	32	78	57.7	5.2
39C	Dec. 28	381	6.03	63	68.5	88	237	3.75	36	65	57.7	4.6
39D	Dec. 28	444	8.68	51	73.0	119	237	4.64	29	66	70.3	
40A	Jan. 1	496	8.95	56	104.0	86	(240)	4.32	32	82	53.8	
40B	Jan. 1	322	5.81	55	86.0	68	(240)	4.34	32	74	58.5	
43A	Jan. 7	318	6.88	46	84.0	82	257	5.56	27	85	65.5	5.8
Average							243	4.52	31	75	60.6	5.2

TABLE II.—SUBJECT, J. H. M.; RESTING EXPERIMENTS LYING FLAT ON BACK

Experiment No.	Date.	Values found in blood flow experiment.					Reduced values.					Ventilation of lungs litres per minute.
		Oxygen c.c. per minute.	Blood flow liters per minute.	Oxygen per liter of blood c.c.	Pulse.	Volume per beat c.c.	Oxygen c.c. per minute.	Blood flow liters per minute.	Co-efficient of utilization.	Pulse.	Volume per beat c.c.	
		a	b	$\frac{a}{b}=c$	d	$\frac{b}{d}=e$	A	$\frac{A}{a}b=B$	C	D	$\frac{B}{D}=E$	
38A	Dec. 23	330	3.56	92.6	74.0	48.1	288	3.10	48	70.0	44.3	5.32
38B*	Dec. 23	390	3.92	99.5	82.6	47.4	288	2.90	52	72.0	40.2	
38C	Dec. 23	374	4.87	76.8	59.6	81.6	314	4.09	40	62.5	65.4	5.98
38D*	Dec. 23	554	8.22	67.4	84.9	96.9	314	4.66	35	70.0	66.6	
42A	Jan. 6	329	4.78	68.8	74.0	64.6	332	4.83	36	72.5	66.6	5.73
52	Mar. 28	437	6.42	68.1	..	..	287	4.22	35	65.0	65.0	6.42
Average							304	3.97	41	69.0	57.0	5.9

* These two experiments were done by the residual method.

We next, with the subject J. H. M., carried out a series of experiments to determine the effect of increasing amounts of muscular work. A bicycle ergometer of the type described by Martin[8] was used. The results are shown in Table III.

TABLE III.—SUBJECT, J. H. M.; WORK EXPERIMENTS

Experiment No.	Date.	Values found in blood flow experiments.					Reduced values.					Ventilation of lungs liters per minute.	Work as recorded by Ergometer kg. meters per minute.
		Oxygen c.c. per minute.	Blood flow liters per minute.	Oxygen per liter of blood c.c.	Pulse.	Volume per beat c.c.	Oxygen c.c. per minute.	Blood flow liters per minute.	Coefficient of utilization.	Pulse.	Volume per beat c.c.		
		a	b	$\frac{a}{b} = c$	d	$\frac{b}{d} = e$	A	$\frac{A}{a} = B$	C	D	$\frac{B}{D} = E$		
W. 2	Feb. 13	1027	9.92	103	100	99	713	6.89	53	100	69	16.3	270
W. 8	Feb. 25	1084	10.77	101	...	..	947	9.41	52	99	95	18.4	410
W. 5A	Feb. 19	753	8.23	91	104	79	852	9.31	47	100	93	17.3	544
W. 5B	Feb. 19	982	13.61	72	102	133	852	11.80	37	95	124	17.3	544
W. 6A	Feb. 22	990	13.04	76	114	114	1060	13.98	39	110	127	20.9	653
W. 6B	Feb. 22	1178	13.65	86	112	122	1060	12.30	45	110	112	20.9	653
W. 4A	Feb. 17	1200	16.77	72	118	142	1075	15.00	37	111	135	20.7	760
W. 4B	Feb. 17	1640	17.60	93	107	164	1075	11.52	48	111	104	20.7	760
W. 7A	Feb. 25	1260	15.15	83	140	108	1404	16.86	43	140	120	26.5	1024
W. 7B	Feb. 25	1300	14.50	90	...	...	1404	15.68	47	140	112	26.5	1024
W. 7C	Feb. 25	1450	14.45	100	136	106	1404	14.00	52	130	108	26.5	1024

In general there was a steady increase in oxygen absorption and blood flow with increasing amounts of work.

Up to about 700 kg. meters of work per minute, the increase in blood flow was met chiefly by an increase in the volume per beat beyond that point by an increase in the pulse-rate. The coefficient of utilization of the oxygen capacity of the blood showed a slight tendency to rise during work.

The effect of caffein during rest was studied in both L. H. N. and J. H. M. The subject, lying flat on the back, received a subcutaneous injection of caffein sodium salicylate. After this at varying intervals two blood flow experiments and a respiration experiment were done. With the subject L. H. N. in two instances, once after gr. v and once after gr. vijss, there was a marked increase in the blood flow and the volume per beat over the resting average, without a corresponding increase in the oxygen absorption, which means that the coefficient of utilization is decreased and that consequently the circulation works less economically. In a third experiment after gr. v, a normal blood flow and coefficient were found, but a somewhat increased volume per beat. With J. H. M. only one experiment was done. This showed an even more marked increase in blood flow and volume per beat, and decrease in coefficient, than was the case with L. H. N.

At the suggestion of Dr. Reid Hunt we did two experiments with the subject J. H. M. upon the effect of caffein during muscular work. The subject received the drug while riding upon the ergometer and a series of blood flow determinations was started about twenty minutes later. No changes which could be interpreted as positive evidence of drug action were found.

The results of all the caffein experiments are collected in Table IV.

Experiments with the Cardiac Subject. C. L., a man, aged thirty-eight years, weighed 63 kgs.

Physical examination showed a heart enlarged both transversely and downward, with a forcible impulse. Double murmurs at the aortic and mitral areas were heard. There was no evidence of decompensation, he was able to do light work without discomfort. There was slight cyanosis. Electrocardiography showed

TABLE IV.—CAFFEINE EXPERIMENTS ON BOTH SUBJECTS

Experiment No.	Date.	Subject.	Values found in blood flow experiments.					Reduced values.					Ventilation of lungs liters per minute.	Work as recorded by Ergometer kg. meters per minute.	
			Oxygen c.c. per minute.	Blood flows liters per minute.	Oxygen per liter of blood c.c.	Pulse.	Volume per beat c.c.	Oxygen c.c. per minute.	Blood flow liters per minute.	Coefficient of utilization.	Pulse.	Volume per beat c.c.			
			a	b	$\frac{a}{b} = c$	d	$\frac{b}{d} = e$	A	$\frac{A}{a} = B$	C	D	$\frac{B}{D} = E$			
31A	Dec. 6	L. H. N.	260	6.97	37	89	78	(240)	6.44	21	83	77	...	0	30 minutes after caffeine gr. v.
31B	Dec. 6	L. H. N.	197	4.5	44	75	60	(240)	5.48	25	60	91	...	0	60 minutes after caffeine gr. v.
37A	Dec. 16	L. H. N.	246	5.93	41	84	71	231	5.57	24	71	78	5.2	0	40 minutes after caffeine gr. vij ss.
37B	Dec. 16	L. H. N.	199	4.45	45	84	53	245	5.48	26	76	72	5.2	0	80 minutes after caffeine gr. vij ss.
43A	Jan. 8	L. H. N.	318	6.88	46	84	82	257	5.56	27	85	65.5	5.8	0	Normal conditions. Done before 43B.
43B	Jan. 8	L. H. N.	310	5.40	57	68	79	261	4.55	33	70	65	6.0	0	25 minutes after caffeine gr. v.
43C	Jan. 8	L. H. N.	426	6.77	63	71	95	261	4.15	36	62	67	6.0	0	65 minutes after caffeine gr. v.
42A	Jan. 6	J. H. M.	329	4.78	69	74	65	332	4.83	36	72	67	5.7	0	Normal conditions. Done before 42B.
42B	Jan. 6	J. H. M.	350	8.67	40	80	108	329	8.15	21	70	116	6.9	0	35 minutes after caffeine gr. v.
42C	Jan. 6	J. H. M.	389	7.55	51	78	97	329	6.40	27	70	91	6.9	0	55 minutes after caffeine gr. v.
W. 9A	Mar. 8	J. H. M.	869	10.5	83	..	..	752	9.12	43	106	86	15.7	372	20 minutes after caffeine gr. v.
W. 9B	Mar. 8	J. H. M.	1090	10.27	106	..	..	752	7.09	55	106	67	15.7	372	30 minutes after caffeine gr. v.
W. 10A	Mar. 23	J. H. M.	1476	19.35	76	..	..	1242	16.30	39	124	131	22.8	916	20 minutes after caffeine gr. v.
W. 10B	Mar. 23	J. H. M.	1644	21.50	77	..	..	1242	16.25	40	128	127	22.8	916	30 minutes after caffeine gr. v.
W. 10C	Mar. 23	J. H. M.	1364	12.55	109	..	..	1242	11.40	56	128	89	22.8	916	40 minutes after caffeine gr. v.

Note: The caffeine was given with equal parts of sodium salicylate. The dosage given below is in terms of pure caffeine.

an aberrant P wave and a prolonged PR interval (the subject had had no digitalis), occasional ventricular premature beats, no left or right ventricular preponderance.

After considerable difficulty the subject was trained so that satisfactory results could be obtained at rest, and later also while riding the ergometer. The resting values for this subject are given in Table V and are strikingly like those of the normal subjects.

TABLE V.—SUBJECT. C. L.; RESTING EXPERIMENTS LYING FLAT ON BACK

Experiment No.	Date.	Values found in blood flow experiments.					Reduced values.				
		Oxygen c.c. per minute.	Blood flow liters per minute.	Oxygen per liter of blood c.c.	Pulse.	Volume per beat c.c.	Oxygen c.c. per minute.	Blood flow liters per minute.	Co-efficient of utilization.	Pulse.	Volume per beat c.c.
		a	b	$\frac{a}{b} = c$	d	$\frac{b}{d} = e$	A	$\frac{A}{a} b = B$	C	D	$\frac{B}{D} = E$
44A	Jan. 15	449	3.31	135	100.0	33	343	2.53	78	72	35
44B	Jan. 15	378	6.03	63	85.0	71	343	5.48	36	72	76
45A	Jan. 18	359	5.65	64	...	...	252	3.96	37	68	58
45C	Jan. 18	245	5.23	47	87.0	60	252	5.39	27	68	79
46A	Jan. 22	329	5.74	57	79.5	72	247	4.30	33	76	57
46B	Jan. 22	372	9.13	41	76.3	120	247	6.06	24	76	80
Average	.....	.....	.....	.....	.....	.....	281	4.62	39	72	64

TABLE VI.—SUBJECT, C. L.; WORK EXPERIMENTS

Experiment No.	Date.	Values found in blood flow experiment.			Reduced values.					Ventilation of lungs liters per minute.	Work as recorded by ergometer kg. meters per minute.
		Oxygen c.c. per minute.	Blood flow liters per minute.	Oxygen per liter of blood c.c.	Oxygen c.c. per minute.	Blood flow liters per minute.	Co-efficient of utilization.	Pulse.	Volume per beat c.c.		
		a	b	$\frac{a}{b} = c$	A	$\frac{A}{a} b = B$	C	D	$\frac{B}{D} = E$		
47	Mar. 10	805	9.02	89	658	7.37	51	100	74	21.0	90
51	Mar. 20	1112	12.85	87	798	9.22	50	100	92	17.4	216
48A	Mar. 12	916	15.17	60	935	15.48	35	96	161	24.4	248
48B	Mar. 12	901	11.65	77	935	12.06	44	96	126	24.4	248
49A	Mar. 15	1156	11.32	102	1050	10.29	59	106	97	21.5	427
49B	Mar. 15	1013	11.99	85	1050	12.40	49	106	117	21.5	427
50A	Mar. 18	1234	13.81	89	1045	11.70	51	114	103	21.4	626
50B	Mar. 18	1311	16.10	82	1045	12.81	47	114	112	21.4	626

The work experiments are shown in Table VI. It was found to be impossible to get this subject to do more than 630 kg. meters of work without considerable distress (fatigue rather than dyspnea), whereas J. H. M. could do 1040 in comparative comfort. The single experiment where the results show a wide divergence from the others (No. 48) was the first work experiment done with the subject and the wide variation was undoubtedly due to the fact that he had not become accustomed to the ergometer and experienced considerable difficulty in peddling properly.

In this subject as in the normal, there is a gradual rise in blood flow and in oxygen absorption with increasing amounts of work. As in the normal, the increase in blood flow is met at first by an increase in volume per beat, later by an increase in pulse-rate.

Blood Oxygen Method. For studying the blood flow in trained subjects the Krogh-Lindhard method is undoubtedly excellent. It is not, however, a method suitable for getting data on a large series of pathological cases, because of the necessity for a large amount of intelligent coöperation on the part of the subject. We therefore have attempted to devise a method by which the blood flow can be studied in untrained subjects and also in moderately sick ones.

We propose the following. The factors directly determined are:

1. The oxygen absorption (this, as before, was done by a short experiment with the Douglas bag).
2. The hemoglobin, and consequently the oxygen capacity (by the Hellige colorimeter as noted above).
3. The percentage saturation of the venous blood with oxygen.
4. The pulse-rate.

The third determination, that of the percentage saturation of the venous blood with oxygen, is obtained by withdrawing a sample of blood from an arm vein into a syringe containing a little potassium oxalate solution, and from which all air bubbles have been expelled. (We also found it well to grease the plunger of the syringe.) From this syringe the blood was directly introduced beneath the ammonia solution in one of the bottles of the Barcroft differential blood gas apparatus, without being exposed at any time to the air. Its percentage saturation with oxygen was thereupon determined.

Having obtained these factors we proceeded to calculate the blood flow. In the light of Barcroft's determinations of the oxygen content of arterial blood,[9] we have assumed that the blood leaves the lungs 94 per cent. saturated. If then the percentage saturation of the venous blood is found to be 60 per cent. the coefficient of utilization of the oxygen capacity will be the difference between the two, or 34 per cent. Knowing the oxygen absorption, the coefficient of utilization, and the oxygen capacity, we calculate the blood flow from the formula:

$$\text{Blood flow per minute} = \frac{O_2 \text{ absorption per minute}}{(\text{coefficient})\ (\text{oxygen capacity})}$$

and the volume per beat:

$$\text{Volume per beat} = \frac{\text{Blood flow per minute}}{\text{Pulse rate}}$$

The accuracy of the method depends entirely upon whether the percentage saturation of the blood in the arm vein is any criterion of that in the right heart. At the present time we are unable to say positively whether this is true, and consequently only propose this method tentatively. We believe, however, that it is a fair criterion, and base this belief in part upon two animal experiments in which we took samples of venous blood from different localities and found a fairly close percentage saturation in the different samples.

Experiment 1. Dog, under urethane, tracheotomized, artificial respiration. Samples of blood taken (within two minutes of each other) from the femoral vein and the jugular vein. The saturation of that from the femoral vein, on blood gas analysis (in duplicate) was 75 per cent. and 68 per cent., average 71.5 per cent., and of that from the jugular vein 71 per cent. and 72 per cent., average 71.5 per cent.

Experiment 2. Dog, under urethane, tracheotomized, natural respiration. Cannula inserted through right jugular vein into right ventricle. Samples taken from the heart through the cannula; also from the left jugular and femoral veins (within three minutes of each other). Blood gas analysis showed the saturation with oxygen of the sample from the heart to be (duplicates) 54 per cent. and 49 per cent., average 52.5 per cent.; of that from the femoral

56 per cent. and 57 per cent., average 56.5 per cent., and of that from the jugular 47 per cent. and 51 per cent., average 49 per cent.

We are quite willing to admit that local vasomotor changes in the arm may alter the local circulation to a marked degree without a corresponding change in the metabolism of the part and consequently alter the local percentage saturation with oxygen of the blood without changing that of the blood in the right heart. For example, the blood from the arm vein in L. H. N. was, under normal circumstances, 52 per cent. saturated on one day, and about ten days later 53 per cent. After his arm had been chilled by immersion for fifteen minutes in water at 10° C., so that it was cyanotic, the saturation was only 23 per cent. If, however, factors which produce local vasomotor changes are eliminated we believe the method to have some value and propose to do further work in the near future, to substantiate this belief.

In Table VII are shown the results obtained by both the Krogh-Lindhard and the blood oxygen methods. In the case of C. L. the agreement is fairly close. In the case of L. H. N. the blood oxygen method gives lower figures for the blood flow and a higher coefficient than the Krogh-Lindhard, but two determinations by the former method done several days apart give very close results. With J. H. M. also the blood oxygen method gives a lower blood flow. This experiment is hardly serviceable for comparison, however, since the subject was probably not normal, having a slight acute infection at the time.

TABLE VII.—COMPARISON OF KROGH-LINDHARD WITH BLOOD OXYGEN METHOD

Subject.	Method.	Oxygen c.c. per minute.	Blood flow liters per minute.	Coefficient of utilization of O_2 capacity.	Pulse.	Volume per beat c.c.
L. H. N.	Krogh (average)	243	4.5	31	75	61
L. H. N.	Blood oxygen	236	3.2	42	73	44
L. H. N.	Blood oxygen	222	3.1	41	78	40
J. H. M.	Krogh (average)	304	4.0	41	69	57
J. H. M.	Blood oxygen	258	2.7	49	80	34
C. L.	Krogh (average)	281	4.6	39	72	64
C. L.	Blood oxygen	255	5.1	29	68	75

In Table VIII are shown the results obtained by the blood oxygen method on four pathological cases. A case of marked hyper-

tension in cardiorenal disease, and a case of Graves' disease with considerable thyroid intoxication showed essentially normal values. Two cases of mitral stenosis, on the other hand, showed very small blood flows and high coefficients. This means a great economy on the part of the circulation in mitral stenosis. To convey the same amount of oxygen to their tissues these patients have to pump considerably less blood than does a normal person. A marked saving must be thus rendered to the heart muscle and we may be compelled to regard cyanosis in such cases as a sign of a compensatory reaction rather than as one of circulatory weakness. It must also be pointed out that the decreased blood flow is not entirely due to improvement in the coefficient of utilization of the oxygen carrying capacity, but also in part to an increase in this capacity as a result of an increase in the hemoglobin.

TABLE VIII.—RESULTS IN PATHOLOGICAL CASES OBTAINED BY BLOOD OXYGEN METHOD

Subject.	Diagnosis.	Symptoms.	Oxygen c.c. per min.	Blood flow liters per min.	Co-efficient of utilization of O_2 capacity.	Pulse.	Volume per beat c.c.	Oxygen capacity (c.c. O_2 per liter blood).
W. E. R.	Cardiorenal hypertension	Slight cyanosis; slight dyspnea; no edema	378	5.5	46	99	55	148
Mrs. M.	Exopthalmic goitre	Marked hyperthyroidism.	304	5.3	28	107	49	202
S. O.	Mitral stenosis (compensated).	No dyspnea; moderate cyanosis.	284	2.2	55	80	27	235
Miss W.	Mitral stenosis (compensated but no reserve).	Marked cyanosis; dyspnea on least exertion.	256	1.3	82	75	17	220

SUMMARY. The volume of the circulation under several conditions has been determined by the method of Krough and Lindhard.

1. In two normal subjects at rest the average blood flow per minute was respectively 4 and 4½ liters.

2. A series of experiments showing the progressive increase in the volume of the circulation up to about 15 liters per minute in response to increasing amounts of work, is presented.

3. The values obtained from a subject with aortic and mitral disease are discussed.

At rest the three pumps act in a strikingly similar manner. During work the damaged pump does as well as the normal as long as the subject is able to do the work.

4. The effect of caffein on the blood flow was studied by the same method in two normal subjects during rest and in one during work. At rest the action of the drug appears to be an increase in the total blood flow and volume per beat without a corresponding increase in the oxygen absorption and hence a diminution in the coefficient of utilization. During work no evidence of any action was obtained.

A method for determining the blood flow applicable to untrained and sick patients is tentatively proposed. It is pointed out that the accuracy of this method depends entirely upon whether the percentage saturation with oxygen of the venous blood from an extremity is a fair criterion of that in the right heart. Two animal experiments which seem to substantiate this view are reported. The blood flows of four pathological cases determined by this latter (blood oxygen) method are reported.

We are indebted to Dr. W. T. Porter for valuable assistance and laboratory facilities for the animal experiments, and to Dr. P. D. White for the electrocardiogram.

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DISCUSSION

Dr. Reid Hunt: Was any explanation found for the variations of the coefficient of utilization?

Dr. J. H. Means: No; we were unable to explain the variations.

ADAMS-STOKES SYNDROME—PERSISTENT BRADYCARDIA, INVOLVING BOTH AURICLES AND VENTRICLES. REMARKABLE PROLONGATION OF THE As–Vs INTERVAL

By W. S. THAYER, M.D.
BALTIMORE

The patient, Mrs. X., aged about fifty-five years, came under my observation on the 27th of April, 1913, in consultation with my friend, Dr. Hardin, of Washington.

At thirteen she had had scarlet fever, and six months later diphtheria, followed by more or less extensive paralysis. In other respects she had been a healthy woman and had had several children. For ten or twelve years, however, there had been some shortness of breath on exertion, and for eight months, frequent bleeding from the nose. For two months she had had peculiar periods of dizziness in which it had been noticed that her pulse was slow and irregular. Two weeks before she had had a sudden attack characterized by loss of consciousness and repeated slight convulsive seizures. Immediately after the attack the pulse was very slow, about 18 to the minute, and fairly regular. On the morning preceding the attack it had been 44; since the attack it had ranged between 28 and 35.

Examination showed a fairly healthy-looking woman lying on her back in bed. The pulse was regular, 36 to the minute. On inspection of the neck, by a rather poor light, there was a well-marked impulse in the jugular with each beat of the pulse, together with a second impulse, occurring at a point about mid-way between each beat. A satisfactory analysis of the jugular undulation was impossible because of the dimness of the light.

The heart was slightly enlarged; the sounds were clear throughout. There was heard, however, between each regular beat, a slight but yet distinctly audible sound. This occurred constantly about mid-way between the regular heart sounds, and had the general character of the sound which one commonly hears in association with the auricular contraction in heart block.

We were inclined to regard the condition as one of heart block with a 2 : 1 rhythm. Tracings were taken which are reproduced in Plates I and II. These tracings show, as may be seen, a bradycardia with an average ventricular rate of 33.7 to the minute. There is but one auricular wave to each ventricular beat. That is, there is a like slowing of both chambers with *a–c* periods of unusual length. In 23 consecutive beats the *a–c* period ranges from 0.65 to 0.82 second in length, averaging, 0.73 second.

The first, and most natural thought that came to one's mind was that this must, after all, be a 2 : 1 rhythm, and that, on careful examination, an elevation corresponding to a second auricular beat might be discovered somewhere on the tracing. And, indeed, rough measurements suggested, at first, that the sometimes prominent notch on the katacrotic limb of the *c* wave might possibly represent the beginning of a second *a* wave. For the differences in the periods separating the obvious *a* waves from the katacrotic notches on the succeeding *c* waves, and those between the latter and the next prominent *a* waves, were so slight that on first glance of the tracings, we were inclined to accept this explanation.

A more careful study, however, shows that the consecutive *a* waves and the katacrotic notches on the *c* waves are not equidistant one from another, the distance from a given *a* wave to the succeeding notch being almost always slightly greater than that from the notch to the following *a* wave. Moreover, the *a* wave is a large, clearly defined elevation and the wave following the notch but slight and sometimes ill-defined. One is therefore obliged to assume that the condition is one of bradycardia involving both auricles and ventricles; and further, the remarkably constant relation between the *a* and *c* waves suggests that the chambers respond to a like impulse conveyed along the usual paths, with a remarkable delay in transmission. The impulse visible in the neck, and the sound

audible between ventricular contractions were clearly associated with auricular systole.

Five weeks later, on the 3d of June, the patient came to Baltimore for further polygraphic and electrocardiographic study. At this time she appeared to be in excellent condition. The pulse was 36 to the minute; the blood-pressure was high, by estimate about 180. In the jugular the same slight impulse was visible between arterial beats, and with the arterial beat no definite presystolic impulse could be seen. The radials were not palpable. The point of maximum cardiac impulse was palpable in the fifth space, about 10 cm. from the median line, the dulness extending about 3 cm. to the right of the sternum. There was no retro-sternal dulness. At the apex there was a slight systolic murmur following the first sound and between beats a soft, short sound was heard. This was loudest at about the juncture of the sixth rib and the sternum on the left, but was audible all over the cardiac area. The liver was palpable on deep inspiration, descending just below the costal margin.

Electrocardiographic records were first taken, after which the patient who seemed a little tired and short of breath, walked slowly up two flights of stairs where further polygraphic tracings were made. The electrocardiograms are reproduced in Plates III, IV and V. They show a bradycardia involving both auricle and ventricle, similar to that recorded in the polygraphic tracing five weeks before.

In lead I (Plate III) the rate of the pulse is 35.9 to the minute, and the average *P–R* interval reaches the remarkable figure of 0.68 seconds. The beats follow one another at regular intervals, and beyond the long *P–R* periods there is little striking about the record. The *P* waves follow one another at regular periods and there is no sign at any point of another *P* complex interfering with *R* or *T* elevations.

In lead II (Plate IV), however, there are several variations from the usual relation and character of the *P* and *R* complexes. In this film the rate of the heart's action is 35.4 to the minute, and the average *P–R* time 0.7+ second.

The *R* wave is inverted and has a rather flat summit with a notch in the middle. The *P* wave is large and triangular in form.

The auricular beats are separated by a period usually varying from 1.6 to 1.7 second. At one point (*w*) after the ninth *R* wave on the record and 1.3+ seconds after the preceding *P* wave, there appears a small inverted deflection which has the general complex of a *P*. This is followed in 0.88+ second at *x*, by an erect *P*, somewhat smaller than the regular auricular complex, and this in turn is succeeded after 0.23+ second at *y*, by an *R* deflection which differs distinctly in form from the ordinary *R* in the tracing. The next *P* follows at *z* after a shorter period than usual—1.08+ seconds—but occurs but little in advance of the time at which it would ordinarily have been due, and has its usual complex. Following this slightly precocious *P* elevation there is an unusually long *P–R* interval—0.88+ second, and the next *P* complex follows after a delay of nearly 0.2 second beyond the ordinary *P–P* interval. The *P* complexes, excepting the two at the points *w* and *x*, are quite similar in form. The *R* complexes occur at practically regular intervals throughout and at but one point (*y*) do they show any variation from their usual appearance.

In lead III (Plate V) in which, unfortunately, but a short film was made, the heart's rate was 35.5 per minute and the *P–R* interval averages 0.69. There is nothing striking about the appearance of this film. The *R* and *T* waves are inverted. The *P* waves are smaller than in lead II, of much the same general appearance as in lead I.

The next record was taken with the Mackenzie polygraph (Plate VI). The patient seemed a little nervous and tired and had walked up two flights of stairs. The pulse rate had become slower—31.3 to the minute. The average *a–c* interval was 0.79+ second. The general appearance of the tracing was exactly similar to that taken on the 23d of April, but at two points slight irregularities were noted, associated, I think, with swallowing or some other movement. At the first of these points (*x*) regular *a* and *c* elevations can be made out, although the former is immediately preceded by an unaccountable wave. The succeeding *a* is separated from the next *c* by an unusually long period. At the second point (*y*) there is an elevation preceding the *v* wave, and the latter is followed by that which appears to be an *a* occurring at a remarkably pre-

cocious period, and separated from the succeeding *c* by a very long space of time. Although no special notes were made upon the tracings at the time when they were taken, the irregularities at *X* were, I think, dependent upon movements of some sort, for I remember distinctly that although the tracings were rather carefully studied, no serious irregularity was noticed at the time. It may be that the elevation at *z* represents a precocious auricular systole similar to those on lead II of the electrocardiogram but I am disposed to regard it as an artefact. Nothing similar was observed on the rest of a fairly long tracing.

Lastly, carotid and jugular tracings were taken with a Verdin polygraph (Plate VII). There was some difficulty in obtaining a satisfactory record. The patient became rather nervous and tired. The rate of the pulse is here 28.8 to the minute, while the *a–c* interval varies from 0.81 to 0.97 seconds, reaching the remarkable average length of 0.886. Excepting for the slower rate of the pulse, and the remarkably long *As–Vs* interval, the tracing differs in no essential from those made with the Mackenzie instrument.

How are we to explain these remarkable records? Are we to assume that we are dealing with an instance of complete heart-block with idio-ventricular rhythm, or are we to fancy that the stimulus for each contraction has developed at the normal point and that we have before us an example of simultaneous slowing of all chambers of the heart with an auriculo-ventricular conduction time amounting in some instances nearly, if not actually, to one second, and with a *P–R* interval which averages between 0.6 and and 0.8 second?

In favor of the former assumption we might regard the rate of the heart, 29 to 35 to the minute, almost exactly that of ordinary idio-ventricular rhythm, as well as the circumstance that in lead II of the electrocardiogram where, at one point, two atypical auricular complexes occur, the ventricular rhythm remains essentially unaltered. But strongly against such an explanation seems to me the circumstance that in a series of tracings taken at an interval of five weeks, the relations of auricular and ventricular contractions remain almost the same. It is hardly conceivable that at such varying periods of time, and in so many tracings, the relation in

and c waves and the P and R complexes should have been so time between the a constant unless auricular and ventricular action were controlled by common stimuli.

Another argument in favor of this assumption would seem to be the character of the R wave in the electrocardiogram. This does not present the diphasic excursions commonly seen with idio-ventricular rhythm, but has rather more the appearance of a complex dependent upon a stimulus carried from above along the bundle.

How may one explain the events on lead II of the electrocardiogram?

The first inverted P complex (w) is probably an auricular extra systole.

How are we to explain the abnormal complexes associated with the following P and R elevations? It would not seem probable that a P–R interval so short as 0.23 second could represent a true conduction time when throughout the rest of the film the P–R interval is never shorter than 0.64 second, unless it be that we fancy that the P elevation here is an extra systole arising in the node or bundle. In extra systoles arising in junctional tissues, the P and R elevations are usually, it is true, much more closely associated. But might not the delay in this instance reasonably be explained by the anomalous conditions which are accountable for the remarkable length of the P–R interval during the regular cardiac action? The suggestion that the P wave at x is an extra systole is supported by the slight variation in its complex, which has already been mentioned.

Following this extra systole, the next regular stimulus, represented by the P elevation at z, occurring after a shorter period than usual and meeting with an exhausted bundle, is followed by an unusually long P–R interval—0.88 seconds.

The variation in the R complex at y suggests, however, another possible explanation. Might it not be that this complex represents an idio-ventricular contraction quite unassociated with the impulse responsible for the preceding P. The sequence of events then might be as follows: A precocious auricular systole at w in a heart in which, owing to disease of the bundle, the P–R time is greatly delayed, finds the bundle refractory and is blocked. At x there

occurs a second auricular contraction at a period fully 0.4 second later than that at which the regular auricular contraction should have occurred. Owing, however, to the long-continued bradycardia at a rate close to that of ordinary idio-ventricular rhythm, the heart is continually on the threshold, as it were, of idio-ventricular impulse formation. And indeed, after a delay slightly longer than usual such an idio-ventricular contraction occurs at *y*, at a period considerably in advanced of the time when the stimulus responsible for the auricular contraction at *x* might have been expected to call forth a ventricular response.

An exceptionally interesting feature of these tracings is the great prolongation of the *As–Vs* interval in the last tracing in which the average *a–c* period was 0.886. On the whole we see a gradual slowing of the pulse from beginning to end of the records taken on the 3d of June, a diminution in the rate from 35.9 to the minute at the beginning of the electrocardiographic records to 28.8 to the minute in the one successful tracing which was obtained with the Verdin instrument; this course of events suggests the possibility that physical exhaustion may have resulted in slowing of the cardiac rhythm and delay in the conduction time.

I have, unfortunately, been unable to see the patient since June, 1913. In July of that year she had two attacks of vertigo with unconsciousness and convulsions lasting several minutes. At the time of the attack the pulse was slow and irregular; immediately afterward it varied from 28 to 50. Dr. Hardin writes me: "In June, 1914, she had three more severe convulsions; one at three o'clock in the morning, another six hours later and another early the following morning. Following these convulsions there was continuous and violent vertigo, markedly increased by raising her head from the pillow, and lasting for eight days.

The next and last attack was on the 17th of February, 1915, when she fell in her bath-room and was unconscious for some time following. I have never seen her in one of these convulsions and have been unable to secure any definite data from any of those who have witnessed the attacks. Her pulse has varied from 28 to 44, when we have seen her during the past winter and she complains almost continually of mild vertigo and a sense of confusion and uncertainty in her head."

We have waited nearly two years before presenting these records in the hope that it might be possible to continue our observations.

Unfortunately, the patient's family have consistently refused to allow further polygraphic or electrocardiographic studies.

It was early felt that it might be well to try the effect of large doses of atropine, but unfortunately the patient shows an unusual idiosyncrasy toward the drug. Dr. Hardin writes, "The minutest dose poisons at once. I have tried it several times when she is unsuspecting. I have seen $\frac{1}{500}$ of a grain (0.00013) of atropine and also 1 drop of the tincture of belladonna flush her face and dilate the pupils so that she cannot see at all, produce great restlessness, insomnia and excitement for hours and hours."

Clinically, the course of events was typically that of an Adams-Stokes syndrome, and it would seem from the history as if at the time of the syncopal and convulsive attacks, there may well have been long intermissions in the pulse. On the two occasions in which we have been able to study the patient, however, there has been no actual auriculo-ventricular dissociation, but a slowing of both auricles and ventricles to a rate of from 28 to 35, about that of the ordinary idio-ventricular rhythm, with a great prolongation of the *As–Vs* interval. The remarkable *As–Vs* interval, as well as the rate of the pulse might lead one to suspect a true dissociation, and the circumstance that in lead II of the electrocardiogram, despite irregular auricular contractions at one point, the ventricle continues its regular rate, might support such an hypothesis.

On the other hand, the constancy of the *As* and *Vs* relations, which remained unchanged for an interval of five weeks, would be almost inexplicable unless we assume that the contractions of both chambers are governed by a common impulse. Again, the *R* complexes are of such a character as to lead one to believe that they are dependent on a supra-ventricular stimulus. The one serious objection to this assumption, that based upon the regularity of the ventricular rate at the time of the auricular extra-systoles in lead II of the electrocardiogram, would not seem to be serious if we regard the ventricular complex at *y* as a single idio-ventricular contraction arising, after a very slight delay, in a heart muscle the rate of contraction of which has been for a long time so slow that it has been continually on the threshold of idio-ventricular stimulus formation—an hypothesis which is supported by the character of the complex.

The unprecedented length of the *As–Vs* interval—*a–c* periods averaging over 0.7 second and reaching at some points nearly, if not quite, one second in duration—*P–R* intervals often exceeding 0.7 second—can hardly be used as an argument against our interpretation of the manifestations. For although we are unaware that *As–Vs* periods so long as this have previously been observed, yet Griffith and Cohn,[1] and Peabody and the author[2] have recorded instances in which the *a–c* interval has amounted to from 0.5 to 0.6 second.

What may be the pathological basis for such remarkable functional manifestations? From the data at hand, it is obvious that one can but speculate. The great lengthening of the *As–Vs* interval and the history of the syncopal and eclamptic manifestations would suggest disease of the *a–v* bundle. But how shall we explain the slow auricular rate? Despite the general regularity of the auricular beats and the persistence of the phenomenon, abnormal vagus influences cannot wholly be ruled out. One might fancy that there were changes which had resulted in a 2 : 1 sino-auricular block, but with the information at hand this can only be advanced as an hypothesis without supporting evidence.

Instances of permanent slowing of the auricular action to a rate below 40 with regularity are by no means common. Such an instance the author had the opportunity to study several years ago.

X, aged thirty years, a civil engineer, consulted me on the 21st of October, 1910, complaining of nausea, dizziness and "sinking spells." He had been a rather heavy smoker, consuming as many, sometimes, as fifteen cigars a day. He had worked very hard at his profession. He had been married four years and had two children.

He had had no serious illnesses in childhood and had never been subject to tonsillitis. As a child he had not been allowed to exercise very vigorously because, as he said, he had not "grown up to his heart." At college he took up rowing, but was generally taken out of the boat for some reason or other before the competitions. He had never suffered from palpitation, dyspnœa or coughing.

[1] Remarks on the Study of a Case Showing a Greatly Lengthened *a–c* Interval with Attacks of Partial and Complete Heart Block, with an Investigation of the Underlying Pathological Conditions, Quart. Jour. Med., Oxford, 1910, iii, 126–151.

[2] A Study of Two Cases of Adams–Stokes Syndrome with Heart Block, Arch. Int. Med., Chicago, 1911, vii, 289–347.

For five years his physician had noticed that his pulse was slow, ranging usually between 44 and 52. Early in May, five months before I saw him, while under an unusual stress of work, he had an attack of vertigo on the golf links which obliged him to lie down upon the ground. After about two minutes he was able to arise and finish the game. A week or two later while at dinner there was a similar attack in which he fell forward onto the table. This was followed by several like attacks at intervals of about ten days, and in the first week in July, he had a very severe paroxysm in the street car. The vertigo lasted while the car was passing about three blocks; he did not fall from his seat. After these attacks he was very weak and felt that he must lie down.

At the time of the attack in the street car he was seen by an excellent physician who found a ventricular rate of 32 to the minute, and what appeared to be a double venous impulse in the neck, suggesting a heart-block with a 2 : 1 rhythm. He then went to the mountains, spending some days at rest. At this time his family physician found his pulse from 32 to 36. In twenty-four hours the pulse had risen to 42. A few days later, on the 15th of July, he had a nervous attack associated with a sense of sinking, feeling very weak, as he expressed it, "as if my blood were all going out." His physician states that his pulse was again 32.

Although there was no history or evidence of lues, he was treated with mercury and iodide of potassium with apparent improvement until the 1st of August, when he had another "sinking spell" which was repeated again two weeks later. At these times the pulse ranged from 28 to 32. The patient suffered also from a feeling of nausea in the morning and felt rather dizzy, but was inclined himself to feel that his dizziness was nervous. From the 15th of August he gradually improved and now, October 21, feels perfectly well.

In my consulting room, the patient appeared a healthy man. Nothing abnormal beyond the cardiac conditions was found. The pulse was between 30 and 35, essentially regular. Now and then a beat occurred at a period a little earlier than it might have been expected, but was followed by no compensatory pause. Inspection of the neck showed a normal venous undulation, all three waves being plainly visible. The patient was a well-nourished man over six feet tall. The heart was a little large, the impulse easily palpable in the fifth space, 11.5 cm. from the median line, slightly within the mamillary line; relative cardiac dulness, 3.3. cm. to the right of the mid-sternum. The first sound was prolonged and followed by a slight, indefinite systolic murmur, heard in the axilla and rather louder over the base; the second sounds were clear and of normal relative intensity. The murmur was less intense in the erect posture, and barely audible at the apex; not heard in the back. The heart was normally mobile; occasionally, as the patient was lying on the left side a third sound could be heard.

Polygraphic tracings with the Mackenzie instrument, showed marked bradycardia involving both chambers of the heart; no extra auricular beats were to be seen; the *a–c* time was normal. The patient entered the hospital for study. A radiographic examination of the chest revealed nothing abnormal.

The urine and blood showed no abnormalities. The Wassermann test gave a negative result. Radiographic examination of the chest showed nothing unusual.

While lying quietly in bed the pulse varied in rate from 28 to 35. The rhythm, though essentially regular, showed, at times, variations consisting of occasional precocious beats suggesting sometimes extra systoles. These beats were not, however, followed by compensatory pauses (Plate VII) and, on the whole, were suggestive of an ordinary sinus arrhythmia.

Respiration was associated with the normal changes in rate, and exercise and emotion accelerated the pulse in the usual manner, but rarely, if ever, to a rate above 50 to the minute. The slight irregularities in rhythm were somwhat more evident after exercise. It is not impossible, as suggested by my colleague, Bridgeman, that this exaggerated irregularity is associated with respiration.

Numerous polygraphic tracings showed little beyond the bradycardia.

The tracing reproduced in Plate VIII, taken when the patient was at rest, shows an essentially regular pulse at the rate of 31.7, with a normal *a–c–v* sequence. The *a–c* interval is a shade long, 0.21 second. In the next tracing taken a little later, after exercise (Plate IX), the rate of the heart is 43.2. The *a–c* interval averages 0.19 second. There is an interesting alternation in the length of the intersystolic periods. This phenomenon was, however, not observed at any other time in our study of the patient. In the following tracing (Plate X) taken after a short pause to adjust the receiving cup over the jugular, the pulse has already fallen to 31.8 and this alternation is no longer evident, while in later records (Plate XI) taken after exercise, no such alternation is seen, although the rhythm shows considerable irregularity.

Atropine 0.0011 (gr. $\frac{1}{60}$) and 0.0016 (gr. $\frac{1}{40}$) administered subcutaneously, produced little or no effect on the heart's action. After 0.0022 (gr. $\frac{1}{30}$) the pulse rate increased gradually to 60. A polygraphic tracing continued for over half an hour after the injection, showed no abnormalities (Plates XII, XIII). It was, unfortunately, impossible to obtain electrocardiographic records as the instrument was out of order.

Since this period the patient has seemed physically well, but the pulse has always remained at a rate between 30 and 40 while at rest. I last saw the patient about two years ago as he was about to go upon the table for an appendectomy. The pulse at this time was 32, and the venous undulation in his neck, perfectly normal. He passed through the operation

without ill effect. His physician, Dr. E. P. Carter, of Cleveland, who has studied the patient carefully and confirmed these observations, writes (July, 1915):

"X is very well, active and busy. His pulse . . . when last taken by me in May, was 39 to the minute. Polygraphic records have never shown any increase in his *a–c* interval. . . . He has had no attacks of dizziness since you saw him."

Here then we have the history of an individual, the rate of whose cardiac action has apparently diminished gradually through a period of years, until five years ago, it reached a permanent rate of but little over 30 when at rest, a rate which has been maintained since that time.

At one period, five years ago, after excesses in work and tobacco, there were several attacks of vertigo and nausea. The pulse, at these times, was a little over 30 and regular. With improvement under rest, there was, however, no change in the rate of the heart's action, and the pulse remains today when the patient appears to be in perfect health, at essentially the same rate. In polygraphic tracings the *a–c* interval is normal and beyond slight sinus irregularities in rhythm which are increased on exercise, nothing of note is revealed.

What are we to regard as the cause of the bradycardia?

It is hardly possible to ascribe it to vagus influences, for experiment shows that the vagus influences are essentially normal. Respiration is followed by the usual variations in rhythm and atropine produces its usual effect *proportionately, however, to the initial cardiac rate.*

One is hardly justified in the present state of our knowledge, in assuming the possibility of a persistent sino-auricular block—an hypothesis against which one might advance further the essential regularity of the pulse through such long periods of time, as well as the gradual increase in rate, without irregularity following atropine. One would fancy that we are here concerned with an essentially slow stimulus formation, with a so-called sinus-bradycardia, a bradycardia depending on chronotropic influences solely.

But in what do such influences consist? Is the condition to be regarded as pathological or only as anomalous?

These are questions which must be answered by time and by further study.

To what were the phenomena of vertigo and nausea due?

The physician who observed the patient at the time of these attacks was at first under the impression that a wave possibly indicating an auricular contraction was to be seen in the jugular between each regular beat.

If this observation was correctly interpreted we must assume that, at this time, there was a true heart-block—a 2 : 1 rhythm. The absence of prolongation of the *a–c* interval is no proof that such a condition may not have existed. One would, however, hardly expect vertigo with a regular pulse of 30 and above, unless this slow pulse followed suddenly on a rate considerably more rapid—unless, say, it were a question of a sudden halving of the pulse rate. May this have occurred at the time of these attacks?

Such an hypothesis might be advanced to explain the phenomena observed in this patient. The author has seen a similar sequence of events in an individual with chronic myocardial disease, whose pulse when at rest, was in the sixties. Any effort, such, for instance, as sitting up and down several times in bed, was followed by a slight increase in the auricular rate with the dropping out of every other ventricular contraction. After a few moments' rest the regular *As–Vs* sequence was resumed. At no time was there any prolongation of the *a–c* interval.

Experimentally, however, in the present case, it was impossible to reproduce any such phenomenon by exercise or atropine, and even with vigorous exercise the pulse rate was never observed at a point above sixty.

It is a question whether the apparent double auricular impulse in the jugular may not, perhaps, have been simulated by the large and very evident *v* wave; indeed, such now is the opinion of his physician who has had the patient constantly under observation.

On the whole the writer is inclined to agree with him and to doubt whether any actual auriculo-ventricular dissociation has ever occurred in this patient. He is disposed to regard the vertigo and nausea as the results of a generally overwrought mental and physical

state in an individual who might well be predisposed to such symptoms because of his anomalously slow heart action.

To what this remarkable bradycardia may be ascribed is a question which, as has been said, cannot definitely be answered.

The phenomena observed in this patient are similar to those described in Mrs. X., mainly, in that in both there is a striking bradycardia involving both chambers of the heart.

In the former patient (Mrs. X.) both the history and the results of physical examination revealed evidences of grave disease of the *a–v* bundle—Adams-Stokes syndrome with extreme slowing and irregularity of the pulse; remarkable prolongation of the *As–Vs* period. In the second patient, however, there was no lengthening of the *As–Vs* interval and, despite the history of vertigo and nausea, there was no convincing evidence that auriculoventricular dissociation had ever occurred. Indeed the symptoms pointed, rather, to an unexplained sinus-bradycardia.

Summary. The history is presented of a woman who, for two years and a half, has had occasional syncopal and eclamptic attacks with extreme bradycardia.

Between these periods the pulse is regular, averaging (in rate) but little over 30 to the minute.

Polygraphic and electrocardiographic study reveals a syncronous slowing of both auricles and ventricles with prolongation of the *As–Vs* interval to a period longer than has hitherto been reported. In polygraphic tracings the *a–c* interval amounts to from 0.7 to 1 second; in electrocardiograms the *P–R* time is often over 0.7 second.

The history of syncopal and eclamptic attacks with great slowing and irregularity of the pulse, as well as the prolonged *As–Vs* interval observed in our studies, justify a diagnosis of disease of the auriculoventricular bundle. The cause of the auricular bradycardia which would appear to depend on an essential anomaly of impulse formation, is not clear.

A second case of apparently essential sinus-bradycardia is reported.

This subject is a seemingly healthy man now thirty-five years of of age. The heart rate for at least five years, has been between 30

and 40 when the patient is at rest. There is no prolongation of the *As–Vs* interval. Exercise, deep breathing, atropine have their usual effects on the heart's rhythm and rate, but proportionately to the initial cardiac rate.

Attacks of vertigo and nausea occurred five years ago, but there is no evidence that these were associated with auriculo-ventricular dissociation. The patient remains in apparently good health despite his persistent bradycardia.

NOTE.—I am indebted to my friend Dr. Bond, of Indianapolis, for the electrocardiograms in Case I.

OBSERVATIONS ON THE USE OF THE DUODENAL TUBE FOR DIAGNOSIS AND TREATMENT

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The duodenal tube for adults was introduced by Einhorn and by Gross about five years ago. A much simpler tube for infants was used by Hess a year or two later

My own use of the tube, which is limited to adults, was begun about two years ago in a rather skeptical spirit, fearing that the instrument was little more than a toy; that its use might be disagreeable to the patient and the results of doubtful value. I was encouraged, however, by finding that men of good judgment in different parts of the country were beginning to use it, and my own experience has convinced me of its value both for diagnosis and treatment.

It is a real contribution to medicine and deserves far greater use than is being made of it now. The field for its use both in diagnosis and treatment is somewhat limited, but it has great value in that field.

The tube was used in 90 cases: in 56 for diagnosis; in 34 for treatment. In this paper we wish simply to emphasize a few of the newer and more important points under three headings: (1) The introduction of the tube, with a study of the factors which help or hinder its passage through the esophagus and stomach; (2) the use of the tube in diagnosis; (3) its use in treatment.

The Introduction of the Tube. In infants the introduction of the tube as described by Hess is a very simple and easy matter. The tube consists merely of a No. 14 or 15 French Nélaton urethral catheter which is not too flexible. Its introduction consists simply in laying the baby on its back on a table and gently but steadily

pushing the tube down the esophagus, through the stomach and into the duodenum in two or three minutes. This prompt and easy passage is made possible by the short, horn-shaped baby's stomach with its small cavity and relative lack of tone at the pylorus. A simple catheter of this kind, unfortunately, cannot be used in the adult, in whom the stomach is large, and the tube wanders far from the pyloric opening. Harmer and Dodd have shown that such a simple catheter or tube in the adult stomach tends to stick to the wall, form loops and curl up.

The introduction of the duodenal tube in the adult stomach is a mild procedure, however, made easy by giving the patient a quarter-grain of codeia an hour beforehand and the use of a throat spray of novocain. Sometimes a few sips of water have been given at the time of swallowing it, but this is unnecessary. A common way of introducing the tube has been to let the patient swallow it in the evening, lie down on the right side and trust the tip of the tube to find its way into the duodenum overnight. This method has largely limited the use of the duodenal tube to patients in a hospital.

Following suggestions from Holzknecht's laboratory, a systematic study was made with the fluoroscope to determine the factors which help or hinder the passage of the tube through the stomach and esophagus in the hope of developing a rapid technic of introduction which could be used with office patients or out-patients of a hospital. We are greatly indebted to Dr. Walter J. Dodd, of Boston, for help and suggestions in the *x*-ray work.

The passage of the tube through the esophagus is a simple matter, started by the swallowing mechanism and then largely helped by gravity in the erect position. It takes place more slowly in the horizontal position by peristalsis alone. The passage of the tip past the larynx is slightly uncomfortable and may make the patient gag. A stylet may be used to push the tip quickly past the larynx into the esophagus, but it is rarely needed. A spasm of the esophagus may, of course, delay the tube; it has not occurred in this series of cases.

In the stomach the factors are more complex. We have studied the effect of gravity, of peristalsis, of the presence of food, of the

rate of feeding in the tube, of the shape of the stomach, and of spasm or obstruction at the pylorus. Gravity was found to have the most important effect in passing the tube rapidly through the stomach, the lesser curvature forms a sloping curve along which the tip of the tube rapidly passes toward the antrum and pylorus, with an empty stomach and the patient in the erect position. If the erect position is continued and the tube steadily swallowed, the tip gravitates to the bottom of the stomach usually in the region of the antrum, and tends to remain there for a time and form a coil in this vicinity. It is possible, however, by putting the patient in different postures and carefully feeding in the tube, to swing the tip to right or left, or forward or back, within the stomach and thus guide it in the desired direction.

The postures used were as follows:

The tube was usually swallowed with the patient erect, which carried the tip vertically down the esophagus to the cardia (about 40 cm.) and half-way down the stomach (about 50 cm.).

For the second position the patient leans forward, slowly lies down on the abdomen and turns on the right side. This carries the tip forward in the stomach and to the right over the high ridge of the spine, and places it in the antrum near the pylorus (tube in 60 to 65 cm.). These postures have been used by Dr. Walter J. Dodd, of Boston, and other radiologists for rapid filling of the first portion of the duodenum with a bismuth meal in horizontal fluoroscopy. They are essentially the same as those used by Holzknecht in passing the duodenal tube.

For the third position the patient turns partly or wholly on the back with pelvis raised by a pillow, to slide the tip up close to the pylorus and help it through (tube in 70 to 80 cm.). This position also raises the hook-shaped stomachs, making them more transverse and easy to deal with, and the high ridge of the spine acts as a watershed and keeps the tip of the tube from dropping back into the left side of the stomach.

The use of a silk-thread guide for the tip has been suggested to help its rapid passage into the duodenum. This means that the patient swallows about a yard and a half of twisted or braided silk thread the day before, which almost invariably finds its way into

the duodenum. The capsule of the duodenal tube is then threaded down over this. While this silk guide is of great help in passing an instrument through a narrow place in the esophagus, it does not help the passage of the ordinary duodenal tube on account of kinking and friction, and, in fact, usually delays or prevents it.

Dr. Frank Smithies, of Chicago, has used a specially made, long, gum-elastic, French catheter with perforated tip, which is passed rapidly into the duodenum over a string guide. The catheter is impregnated with metallic salts, is easily seen with the fluoroscope, and the position of the tip in the duodenum verified. He has found this a successful, rapid method of aspirating the duodenal contents. I have had no opportunity to use it through inability to get the French catheter.

The chief types of duodenal tube differ somewhat in their size and the weight of the tip, and vary also in the speed with which they can be passed through the stomach, largely on account of the action of gravity on the tips of different weight.

The Einhorn tube is small, with No. 8 French tubing, with a long, oval, perforated tip of about 50 grains weight.

The Gross tube is much larger with a soft No. 20 French tube and a large, heavy tip of about 150 grains weight covered with rubber.

The Palefski tube is like that of Einhorn, but has a heavier, shorter, oval tip weighing about 100 grains with only a few perforations.

The heavier tips can be more readily placed close to the pylorus than the light ones by the action of gravity and the posture of the patient, and for this reason the Gross tube and the Palefski tube, as a rule, enter the duodenum more rapidly than the Einhorn tube.

Each tube has its advantages. The Einhorn tube is small, easily swallowed, easy to retain, usually passes more slowly into the duodenum than the others, and occasionally plugs with mucus. We used it entirely for treatment and, frequently, for diagnosis.

The tube with the Palefski tip is likewise small, easy to swallow and retain, passes more rapidly into the duodenum, as a rule, but on account of fewer openings in the tip, makes the aspiration more difficult at times than the Einhorn tube. This tube gave the best results for rapid aspiration of duodenal contents for diagnosis.

The Gross tube is only used for diagnosis. It enters the duodenum readily and is easy to aspirate on account of its large size, but the rubber-covered tip is rather large and clumsy and the tube is decidedly harder to swallow and retain. For these reasons we have not used it much.

The position of the end of the tube was determined either by the fluoroscope or by the milk test. The latter consisted in giving the patient a few swallows of milk and then aspirating gently through the tube after a minute. If the tip of the tube is in the stomach, the milk promptly returns through the tube; if the tube has passed through the pylorus into the duodenum, the pylorus has almost always closed about it and no prompt aspiration of the milk is possible. This is the simplest clinical method of determining the position of the end of the tube for routine work and is reliable in almost all cases. If the pylorus is relaxed, the milk may pass promptly into the duodenum and be aspirated through the tube, and thus the tip appears to be in the stomach when it actually is in the duodenum. This has rarely happened in my experience. Of course, the presence of some pancreatic ferments is not evidence in itself that the tube is in the duodenum. These may be obtained above the pylorus at times.

Results. The tubes reached the duodenum in about 30 per cent. of the cases within fifteen minutes; in about 30 per cent. more within a half-hour, and in about 20 per cent. more of the cases within one to six hours. In about 20 per cent. of the patients the tube had to be left in overnight in order to reach the duodenum.

Some difficulties were met in adapting the routine to different sizes of patients and different sizes and shapes of stomachs. The chief causes of delay was coiling up of the tube in the stomach if fed in too fast; and dropping back of the tip into wrong positions if fed in too slowly, especially, dropping back into the left side of the stomach, and to the left of the high ridge of the spine, when the patient turns from a right lateral position upon his back. Peristalsis was found to have little effect on the rate of passage of the tube through the stomach until the tip is close to the pylorus, then peristalsis pushes it through. Food delayed the passage of

the tube through the stomach, largely by interfering with the action of gravity and the rapid placing of the tip close to the pylorus. The tube could be passed through the empty stomach by the aid of posture in about a half-hour in the majority of cases; the presence of an ordinary meal would delay the passage of the tube three or four hours, or even more.

The rate of swallowing the tube affected the time of its passage through the stomach. This was more easily controlled in the tubes with a heavy tip. The tube passed on more steadily if it was swallowed at a rather slow rate. It was important not to try to feed it in too rapidly, for the tube tends to get ahead of the capsule, and kink or roll up, and delay its passage; it was desirable to have very little slack, but to have the capsule move along steadily ahead of the tube. This was best arranged as a routine by swallowing the tube to the 50 cm. mark in the erect position; then slowly into 60 or 65 cm. in the second position; then slowly in to 70 or 75 cm. in the third position, taking about five minutes in each position.

The shape of the stomach had a definite effect upon the rate of the passage of the tube. The high, transverse, so-called "horn-shaped" stomachs hastened the passage of the tube; the vertical, hook-shaped, relaxed, and low stomachs delayed its passage from half an hour to an hour or more in the more marked cases.

Obstruction of the pylorus due to spasm or organic disease naturally delayed the passage of the tube, and in marked cases may render the test impossible by keeping the tip in the stomach. Fortunately, these conditions were rarely met with in the type of cases where the tube was used for diagnosis; where the spasm was associated with hyperacidity it was easily relaxed by the use of alkalies or atropin.

The practical application of the above data is as follows: the quickest way to enter the duodenum is to get the tube close to the pylorus within a short time. This is best accomplished by using a light tube with a heavy tip swallowed by the fasting patient in the erect position, feeding the tube in slowly and steadily and taking about five minutes in each of the three positions described.

From the above data it is seen that the attempt to develop a rapid method of passing the tube into the duodenum has proved a partial success. More than half of the cases were quickly intubed. In a number of cases this was not possible, even with the use of the heavy-tipped tube, and it was necessary to let the patients lie on the right side for several hours or more to reach the duodenum. In short, the quick method saves much time and usually works; the slow method was, however, more reliable, and always used if the first failed. Since so much depends upon a negative test for ferments in diseases of the pancreas, we must be sure that the tube is in the duodenum, and not in the stomach, and for this reason all negative results should be repeated using, preferably, the slow method of introduction and the Einhorn tube. The rapid introduction of the tube is a more expert procedure than the slow, overnight introduction and requires more attention on the part of the physician, but I have usually found that a nurse could handle the tube satisfactorily after a little experience and with careful directions.

Diagnosis. The tube was introduced by the rapid or slower methods described. Duodenal juice was taken one to two hours after a drink of clear tea with sugar, to stimulate secretion. It was aspirated with a syringe or rubber bulb and examined for ferments, bile and sediments after noting its color, appearance, and reaction to litmus. If not examined at once it was kept on ice a few hours. The Gross-Fuld test was used for trypsin, the Wohlgemuth test for amylase, and the ethyl butyrate test for lipase.

On the advice of Professor Folin and of Professor Mendell, these ferment tests were chosen as being decidedly more accurate and satisfactory than the use of Metts tubes as described by Einhorn. Delicate chemical tests for blood seemed out of place.

The technic of the tests was as follows: In the test for trypsin we determined what dilution of the duodenal juice would completely digest 10 c.c. of 0.1 per cent. casein solution in one hour in a water-bath at 37° C. 1 c.c. of duodenal contents was diluted with 99 c.c. of water. In several test-tubes were placed 0.1 c.c., 0.2 c.c.,

1 c.c. and 2 c.c. respectively of the diluted contents. To each tube was added 10 c.c. of a 0.1 per cent. alkaline casein solution. The dilutions were $\frac{1}{10000}$, $\frac{1}{5000}$, $\frac{1}{1000}$ and $\frac{1}{500}$ respectively of the duodenal juice. In cases of suspected pancreatic disease dilutions of $\frac{1}{100}$ and $\frac{1}{10}$ were made. After one hour's digestion a little 0.5 per cent. acetic acid was added to each, to precipitate undigested casein. Under normal conditions the $\frac{1}{10000}$ dilution usually became cloudy with undigested casein and the other three dilutions remained clear. Occasionally the $\frac{1}{50000}$ dilution became slightly cloudy. Clouding of the $\frac{1}{1000}$ or $\frac{1}{500}$ dilution showed absence or very marked diminution of trypsin.

In the test for lipase we determined the acidity developed by the digestion of 1 c.c. of ethyl butyrate by 1 c.c. of undiluted duodenal juice in twenty-four hours at 37° C., in terms of cubic centimeters of $\frac{N}{20}$ NaOH. Into each of two test-tubes was placed 1 c.c. of duodenal juice, one was boiled for control. To each tube was added 1 c.c. of neutral ethyl butryate, 10 c.c. of distilled water and 1 c.c. of toluene. These were placed in an incubator at 37° C. for twenty-four hours, then both titrated with $\frac{N}{20}$ NaOH, using phenolphthalein as indicator. The result in the control tube was subtracted from the other to give the final result.

In the test for amylase we determined the number of cubic centimeters of 1 per cent. starch solution digested by 1 c.c. of duodenal juice in one hour at 37° C. In each of five small test-tubes were placed 5 c.c. of a 1 per cent. starch solution. 1 c.c. of the duodenal juice was diluted with 1 c.c. of water and 1 c.c., 0.5 c.c., 0.2 c.c. and 0.1 c.c. of the diluted juice were added respectively to four of the test-tubes. The fifth tube served as a control. The tubes were incubated at 37° C. for an hour and then tested for undigested starch with Lugol's solution. The last tube of the series which failed to react was the one from which the reading was taken. The ferment activity is expressed in the number of cubic centimeters of starch solution 1 c.c. of undiluted juice can digest. If it takes 1 c.c. of juice to digest 5 c.c. of starch, the activity is 5; if digestion is accomplished by 0.5 c.c., it is 10, etc. The activity figures for the four tubes diluted as above are 10, 20, 50 and 100.

TABLE OF ANALYSES OF DUODENAL SECRETION

No.		Amount.	Appearance.	Color.	Reaction.	Trypsin.	Lipase.	Amylase.
	NORMAL AND MISCELLANEOUS DISEASES.							
1	Normal	19	Cloudy	Golden	Neutral	1/1000	0.4	20
2	Normal	5	Clear	Golden	Neutral	1/500	0.6	20
3	Normal	20	Clear	Golden	Neutral	1/5000	2.4	20
4	Normal	15	Clear	Golden	Neutral	1/5000	1.2	50
5	Normal	20	Clear	Golden	Neutral	1/500	2.6	20
6	Tuberculosis of lungs	10	Clear	Golden	Slightly acid	1/5000	2.9	0
		12	Clear	Golden	Slightly acid	1/1000	3.6	0
7	Neurasthenia	10	Cloudy	Golden	Slightly acid	1/5000	0.7	10
		25	Cloudy	Golden	Neutral	1/10000	1.5	20
8	Neurasthenia	10	Cloudy	Golden	Neutral	1/5000	1.7	10
		12	Cloudy	Golden	Slight acid	1/1000	2.0	0
9	Pernicious anemia	22	Clear	Golden	Neutral	1/1000	2.5	10
		17	Clear	Golden	Neutral	1/5000	1.5	50
10	Chronic arthritis	19	Clear	Golden	Slightly alkaline	1/5000	0.9	20
		7	Cloudy	Golden	Slightly alkaline	1/1000	0.9	100
11	Chronic appendicitis	30	Cloudy	Golden	Neutral	1/1000	9.6	50
12	Nervous vomiting	10	Clear	Golden	Neutral	1/5000	3.9	20
13	Nervous vomiting	14	Clear	Golden	Neutral	1/5000	4.5	50
14	Constipation	24	Clear	Golden	Neutral	1/1000	2.0	10
15	Constipation	24	Clear	Golden	Neutral	1/1000	4.0	50
	DISEASES OF THE STOMACH.							
16	Chronic gastric ulcer	20	Clear	Golden	Neutral	1/1000	0.4	100
		15	Clear	Golden	Neutral	1/5000	0.7	0
17	Chronic gastric ulcer	20	Clear	Golden	Neutral	1/5000	0.4	100
		7	Clear	Golden	Slightly alkaline	1/10000	0.5	100
18	Duodenal ulcer	7	Clear	Golden	Neutral	1/5000	1.2	0
		5	Clear	Golden	Slightly alkaline	1/1000	0.7	10
19	Gastric ulcer	27	Cloudy	Yellow	Slightly acid	1/10000	0.4	0
		30	Cloudy	Yellow	Slightly acid	1/10000	0.3	20
20	Duodenal ulcer	15	Clear	Yellow	Neutral	1/10000	2.4	20
		10	Clear	Yellow	Neutral	1/10000	2.0	20
21	Gastroptosis	12	Clear	Yellow	Neutral	1/1000	2.0	0
22	Gastroptosis	9	Clear	Yellow	Neutral	1/5000	1.0	10
23	Gastric ulcer	7	Cloudy	Yellow	Neutral	1/5000	0.5	100
24	Chronic gastritis	3	Clear	Yellow	Neutral	1/1000	2.4	50
25	Gastric atony	10	Cloudy	Yellow	Neutral	1/10000	0.9	50
26	Gastric atony	20	Clear	Yellow	Neutral	1/1000	3.5	50

27	Gastric neurosis	5	Clear	Golden	Neutral	0	0.2	0
		14	Clear	Golden	Neutral	1/5000	4.7	20
28	Gastric neurosis	10	Clear	Golden	Neutral	0	1.9	0
29	Chronic gastritis	35	Clear	Yellow	Neutral	1/1000	5.0	20
30	Chronic gastritis	15	Cloudy	Yellow	Neutral	0	0	0
		13	Cloudy	Yellow	Neutral	0	1.9	0
31	Achylia	15	Clear	Golden	Neutral	1/5000	1.2	50
32	Achylia	25	Cloudy	Golden	Neutral	1/10000	1.5	20
33	Achylia	30	Cloudy	Golden	Neutral	1/10000	9.5	50
	DISEASES OF THE PANCREAS.							
34	Cancer of head[1]	5	Cloudy	Yellow	Alkaline	0	0	0
		8	Cloudy	Yellow	Alkaline	0	0	0
35	Chronic pancreatitis	8	Slightly cloudy	Yellow	Neutral	0	0.4	0
		19	Slightly cloudy	Grayish	Neutral	0	0	0
36	Cancer of head[1]	30	Cloudy	Gray	Neutral	1/10000	1.5	50
		2	Cloudy	Gray	Neutral	1/10000	0.8	20
37	Cancer of head[1]	10	Slightly cloudy	Yellow	Alkaline	1/10000	2.1	50
		30	Slightly cloudy	Yellow	Alkaline	1/5000	3.1	20
38	Chronic pancreatitis[2]	17	Slightly cloudy	Yellow	Neutral	1/1000	2.2	0
		13	Clear	Golden	Neutral	1/1000	2.0	0
39	Cancer of head[2]	19	Cloudy	Watery	Neutral	0	0	0
		8	Cloudy	Watery	Neutral	0	0	0
	DISEASES OF THE LIVER.							
40	Cancer of gall-bladder[1]	10	Cloudy	Yellow	Slightly acid	1/1000	1.6	0
		5	Cloudy	Yellow	Slightly acid	1/500	1.5	0
41	Catarrhal jaundice	9	Cloudy	Yellow	Neutral	1/1000	0.2	100
42	Alcoholic cirrhosis	10	Cloudy	Yellow	Neutral	1/1000	0.2	20
		14	Cloudy	Yellow	Neutral	1/1000	...	100
43	Alcoholic cirrhosis	15	Clear	Yellow	Slightly alkaline	1/10000	1.6	100
44	Catarrhal jaundice	10	Cloudy	Yellow	Neutral	1/10000	6.0	100
		30	Cloudy	Yellow	Neutral	1/10000	...	50
45	Gall-stones[1]	20	Cloudy	Yellow	Slightly acid	1/5000	0	20
		50	Cloudy	Yellow	Slightly acid	1/1000	8.0	50
46	Gall-stones[1]	30	Cloudy	Greenish	Neutral	1/10000	3.5	50
		31	Clear	Golden	Neutral	1/5000	0.5	10
47	Gall-stones[1]	15	Clear	Golden	Neutral	1/10000	0	50
		12	Clear	Golden	Neutral	1/10000	3.0	50
48	Cancer of gall-bladder[1]	10	Cloudy	Yellow	Neutral	1/5000	1.5	50
		6	Cloudy	Yellow	Slightly alkaline	1/1000	1.5	50
49	Cancer of bile ducts[2]	8	Cloudy	Yellow	Neutral	1/500	0	0

[1] Operation. [2] Autopsy.

In only 7 out of 56 cases did we fail to get duodenal juice for examination. We could not get the tube into the duodenum in 3 cases on account of pyloric obstruction, and in 1 case on account of marked gastroptosis and atony; in 3 cases the tube plugged persistently with mucus and the attempt was given up. In most cases aspiration was prompt and easy. In a few, careful technic and repetition of aspiration or washing out of the tube were needed. The tube is as safe as the ordinary stomach-tube, perhaps safer, and is much less disagreeable. Gentle aspiration never gave trouble. The duodenal juices were tested as controls in a series of normal and miscellaneous cases, including cases where the tube was used for treatment. The results are tabulated.

The color was usually yellow, golden, or greenish, and its chief value was to indicate the presence or absence of bile. The juice was usually clear, but often cloudy in cases without known disease of the duodenum or bile passages, and was usually cloudy in diseases of the liver or pancreas. The reaction was usually neutral or slightly alkaline, but often was slightly acid from the presence of gastric juice. It is often stated that the reaction in the duodenum is alkaline; this is not the case. The reaction depends on the combination of alkaline pancreatic and intestinal juices with the acid gastric secretion. They may neutralize each other and there is occasionally an excess of acid.

Gross blood was found only in 2 cases of cancer of the pancreas.

Tests for bile have little value: various tests were used, modifications of Huppert's and Rosin's tests, without getting accurate results. The simple tests were rough, the elaborate tests little better. Practically, as much could be told by the color of the duodenal juice as by the tests.

A positive test for bile in the duodenal contents is the surest and best proof that the ducts are, at least, partly open. A negative test for bile cannot be taken as absolute proof of closure of the ducts owing to the unsatisfactory nature of the present tests.

The results of the ferment tests showed much apparent variation in different cases and from day to day in the same cases. There are several factors which account for this: (1) the variation in the reaction of the juices; (2) the dilution of the pancreatic juice

with the gastric juice and with more or less bile, and (3) the lack of strictly quantitative methods of analysis. On this account only marked diminution or absence of ferments has value in diagnosis.

Our results are, in general, an agreement with those of previous observers. It is unfortunate that details of analyses and methods of recording results by different men vary so much that there is some difficulty in comparing their results. Some of the apparent accuracy of tables of ferment analyses is really fictitious.

The three ferments, trypsin, amylase, and lipase, usually varied together, but of the three, trypsin was the most constant and reliable, the lipase next and the amylase last, the latter being occasionally absent when the other ferments were normal in cases without known pancreatic disease. In Einhorn's cases trypsin was occasionally missed when other ferments were present; I believe this is due to the use of a less accurate method. In our cases, tests for all three ferments were made for completeness, but for clinical purposes the test for trypsin has far the greatest value, and it seems as if the examination might be simplified by omitting tests for the other two ferments without losing much. Amylase and lipase were never both present when trypsin was absent.

Examination of the sediment usually proved of little value.

Diseases of the Pancreas. The examination of the duodenal juice is the most direct and valuable test we have of the pancreatic secretion. It is easy in most cases to get the juice for examination, and the results are apparently quite accurate, far more so than in other tests. It avoids the many variable factors and great technical difficulties in the use of other methods, such as the Sahli glutoid capsule and Schmidt's nuclear tests, the use of the oil test-meal, tests of the *feces* for ferments, and other indirect methods.

It is better to examine the duodenal contents for pancreatic ferments rather than the feces; in the same way it is better to test the stomach contents for rennet and for pepsin rather than the stool. In the feces we have pancreatic ferments mixed with non-pancreatic ferments, such as bacterial, leukocytic and other cellular ferments, as well as intestinal lipase and erepsin. In addition we cannot tell how much pancreatic ferment has been absorbed or used up in the small intestine.

In our cases (with one exception), adults without known pancreatic disease, all had active trypsin. Or, to put it another way: *Constant* marked diminution or absence of trypsin was found (with one exception) only in known pancreatic cases, of which we have 6, namely: 4 cancer, diagnosed by operation or autopsy; 2 chronic indurative pancreatitis diagnosed, 1 by autopsy and 1 by characteristic history, feces, and physical examination. We have included only proved cases of pancreatitis in our series. We consider the mere "feeling a rather hard gland" by the surgeon at operation as very poor evidence.

Chronic jaundice, cachexia and chronic ill-health may lessen secretion somewhat, but rarely below normal limits. A negative test has definite value in diagnosis; a positive test (presence of ferments) does not rule out pancreatic disease. In 2 cases of cancer of the pancreas with palpable tumor, ferments were present.

In 1 or 2 pancreatic cases the absence of ferments was clearly shown by ordinary chemical and microscopic examination of the feces after the Schmidt-Strassburger test diet. In others, particularly where jaundice was present, the tests of the duodenal juice were much more definite.

We must admit that pancreatic cases with little loss of function are very hard to diagnose by any method and that cases with very marked loss of functions are often obvious without any very special tests, but between these is a wide middle ground where the duodenal tube is the most accurate and valuable method of diagnosis. Einhorn's elaborate classification of five varieties of pancreatic secretion, normal, increased, diminished, disturbed and variable pancreatic secretion (eu-, hyper-, hypo-, dys-, and heteropancreatism), determined by analyses of the duodenal juice, does not rest on a firm basis for the reasons given above. The Metts tubes, which he has largely used, are convenient and useful for qualitative tests but unreliable for quantitative work.

Diseases of the Liver. Here the use of the tube has less clinical value. It is probably the best method we have of deciding whether the bile passages are completely or partly closed, by noting the presence or absence of bile in the duodenal juice. Unfortunately this value is much limited by the lack of a good test for bile. Posi-

tive tests have value; negative tests are doubtful. The presence of bile in the duodenal juices is the best proof we have that the common duct is, at least, partly open. Several times bile was found in the duodenal juice when there was none in the feces. In most of the normal and miscellaneous cases, bile was present. In most of the benign diseases of the liver, such as gall-stones, cholangitis, and cirrhosis, even when jaundiced, bile was also present. In most of the cases of cancer involving the bile passages bile was not found. In short, we may say in the jaundiced cases, that the presence of bile in the duodenal juice favors benign disease, and repeated absence favors malignant disease. There are so many exceptions, however, that the test has little value in the diagnosis of the individual case.

Our cases are too few for conclusions. Crohn, from a larger experience, has found bile almost always present in impacted gall-stones even with long jaundice, and almost always absent in jaundice due to growth, and therefore concludes that complete absence of bile from the duodenal juice is a valuable sign of local cancer. We cannot agree with this on account of the variability of the bile tests in the duodenal juice.

In normal cases not much sediment or flaky mucus is found: we usually got a ropy, greenish fluid which may be clear or cloudy; on the other hand, in cholecystitis or duodenitis we have sometimes found turbidity, mucus, or pus cells; gall-stone sand was found in one case of gall-stones. These signs have seemed rather uncertain guides in diagnosis, and, as in diseases of the stomach, I believe sediments have minor importance.

Diseases of the Stomach. I have used the duodenal tube frequently for obtaining stomach contents in place of the usual stomach-tube. It takes about a minute longer to get in than the usual stomach-tube, which can be quickly pushed down, but once past the larynx it is far more comfortable and the patients sit quietly as long as desired while the stomach contents are aspirated. It can be retained and used for examinations of the gastric secretions at intervals of fifteen to twenty minutes according to the method of Rehfuss.

The pancreatic ferments in the miscellaneous stomach cases were normal save in 2 cases. One case of gastric neurosis showed almost

complete absence of ferments on the first examination and normal ferments on the second. One case of chronic gastritis showed almost complete absence of ferments on two examinations. I have no satisfactory explanation. It is worth noting that in 3 cases of achylia gastrica the pancreatic ferments were normal. This accords with previous data in showing how little pancreatic secretion depends on gastric acidity.

Treatment. The duodenal tube of Einhorn was found very useful in a limited group of cases. It is not a method of treatment to be used as a routine in any large number of diseases of the stomach or bowel; it is a method for the exceptional case and its use should be limited strictly to these. In this way we avoid using the tube when a simpler method of treatment would be better and we are able also to obtain brilliant results in suitable cases which do not yield to other methods of treatment.

Many physicians have passed judgment on the tube without even using it, and have been afraid to try it for fear of its discomforts would outweigh its benefits or because they believed they could get as good results in other ways. The discomforts of the tube are very moderate; it is not difficult or painful to swallow; the presence of the tube in the throat is slightly disagreeable, but makes no real trouble, and after the first few hours the patient gets accustomed to its presence. It is much smaller than the smallest stomach-tube; the irritation in the throat is trifling and does not keep the patient awake at night. It has surprised many physicians to see the contented, happy faces of patients who are having duodenal feeding.

The use of the duodenal tube is often the best way to rest the stomach and keep the patient well fed. The skeptic finds this hard to believe, but it is true. I have repeatedly seen the same food taken with perfect comfort through the tube, which caused distress and vomiting when taken by the mouth. It is a safe, sensible method of treatment for a selected group of cases and deserves more general use. We are able to supply abundant food at the point in the digestive tract where it is easily digested and absorbed, and, also, to maintain nitrogenous equilibrium. This is the only form of artificial feeding in which it is possible to keep the balance

of nitrogen. This is a marked contrast to rectal feeding, where hardly anything is absorbed except water and sugars, where only about one-tenth the necessary nitrogen can be given, and only about one-fourth the necessary food. With rectal feeding the patients lose weight rather rapidly as a rule; with duodenal feeding the patients almost always keep their weight and often make good gains in weight. With rectal feeding we can get in about 500 calories; with duodenal feeding usually 1500 to 2000 or over. The tube is not used more than a week or two, and then, with vomiting stopped and nutrition improved, rest and feeding by mouth follow.

An important use of the tube is in cases of persistent vomiting, "medical cases" in nervous, exhausted persons, including pregnant women, where a reflex or toxic cause has upset the stomach seriously. I have restricted the use of the tube here to the worst cases, which resisted other forms of treatment, and used it as a last resort. Now I use the tube earlier and more often than at first. There were some failures, of course, but more brilliant results. I have not used the tube in "surgical cases" of vomiting, with obstruction, or immediately after operation.

Another important group are cases of severe malnutrition with loss of appetite and perhaps vomiting, with low, atonic stomachs which are dilated and unable to empty properly. This indication is not new, but I wish specially to emphasize it, as some of the most striking results have been obtained in this class.

Gastric and duodenal ulcer is another group of importance. Here opinions have differed greatly as to the value of the tube. Some men have felt that it is the best of all treatment for ulcer when the tube is well borne; that it should be used in practically all uncomplicated cases; that it saves time and increases the percentage of recovery. It is used on the theory that an ulcer heals better in a well-fed person with an empty stomach than in a starving one or one whose stomach is doing the work of digestion.

Others use the tube only after other treatment has failed; others think that those cases which do not yield to ordinary medical treatment should go directly to the surgeon; that the tube might distinctly harm the patient by causing hypermotility and secretion, the two very things we wish to avoid in treating ulcer.

It is still a question how often to use the tube in ulcer. I have been quite conservative and used it only in a small group of cases, namely, in those which had resisted other medical treatment and in which no marked deformity or obstruction was present. The presence of hemorrhage, even if considerable, has not proved a counter-indication.

I have also used it in cancer of the esophagus to relieve and prevent starvation. Here the tube had to be pushed down by means of a stylet over a silk-thread guide.

Other less urgent indications have been proposed, such as lavage of the duodenum in duodenal catarrh, gall-stones, chronic jaundice, or cirrhosis of the liver, for the purpose of washing out inflammatory or infectious particles; also for disinfection of the bowel by inflation of oxygen through the tube. I have not felt that the indications were clear for the use of the tube in this group.

The Technic of Feeding. This has been well described by Einhorn and Morgan from their large experience; their papers should be read. I am especially indebted to Dr. Morgan and Dr. Charles G. Stockton, of Buffalo, for valuable suggestions. There are many details of technic which must be kept in mind in order to get the best results and make the treatment a success.

We have used the Einhorn tube exclusively for treatment, as here the patient is in bed and there is no special need for great speed in introducing the tube, and it is easy to retain for the period of treatment which often lasts a week or two. It is sometimes desirable to use an extra long tube, of 100 to 125 centimeters, which will pass about 25 centimeters beyond the pylorus. This was used in certain vomiting cases to prevent regurgitation or vomiting of the tube, and in duodenal ulcer it is well, also, to have the tip of the tube well below the ulcer.

Various special syringes have been devised for introducing food through the tube. They are all unnecessary; the simplest apparatus is the best, and consists of a glass reservoir or can with a hole in the bottom, a rubber tube provided with a clamp, and a glass drop tube such as is used for the Murphy drop method of giving fluids by rectum. I first used a thermos bottle as a reservoir to keep the food at a constant temperature, but found that this was

unnecessary. The duodenum is more sensitive to heat than to cold and the main thing is not to have the food too hot. It should be 98° to 100° F.

The food is given slowly, 50 to 60 drops a minute, so that the feeding takes usually from twenty to thirty minutes. The rate of flow depends upon the patient; some require twice as long as others for a feeding. Patients should be watched at first during the feeding for nausea or discomfort until a comfortable rate of feeding is found. In this time the food in the reservoir cools only a little and is easily warmed before reaching the duodenum by passing down the long esophagus. If any additional warmth is required in a cool room, this is easy to arrange by placing a hot-water bag over the tube in bed between the reservoir and the patient. The pressure from the reservoir, hung two or three feet from the patient's head, easily forces the liquid food through the duodenal tube if the latter is kept clean.

The standard foods for use through the tube are milk, eggs, cane-sugar or milk-sugar, and cream. It is better to strain the liquids that are used through several thicknesses of gauze. Eggs should be stirred up in the milk, not beaten. Milk-sugar often irritates the bowel and has to be used sparingly or omitted. The best way is to begin with milk alone or mixed with egg and not use the milk-sugar until after a week. Eggs are sometimes not borne well; it is often well not to begin to use eggs for four or five days, then a half of one egg may be added to every other feeding, and a few days later to each feeding. Cream may be given, from one to three ounces, every other feeding. Broths are not very useful; they have little food value and may clog the tube.

Eight feedings a day at two-hour intervals are the rule, beginning at 7 A.M. and ending at 9 P.M., starting with two or three ounces and increasing to six or eight ounces on the second day and eight or ten on the third. *It is very important, after each feeding, to inject an ounce of warm water through the tube to wash it out, then a syringeful of air to drive out the water, and then to turn the stopcock in the tube* so that no milk can run back to the tube and coagulate and clog it. Before feeding, inject one syringeful of air into the tube to empty it. It is very easy to keep the tube clean and in good working order if these directions are followed.

The tube is easily kept in position with a small piece of adhesive plaster fastened to the cheek. It is well to move the tube from one side of the mouth to the other once a day to avoid irritation. The mouth must be kept clean with a mouth wash.

It is better to test occasionally to see that the tube is in proper position; give the patient a few swallows of equal parts of milk and water by mouth and then aspirate at once through the tube; if the withdrawn liquid is milky, the tube probably is not in the duodenum; if clear yellowish or greenish, it is in the duodenum.

Results. The tube was used for treatment in 34 cases, namely: 10 with malnutrition, gastroptosis, and atony; 10 of persistent vomiting; 14 of gastric or duodenal ulcer. The group of cases is too small to warrant any sweeping conclusions. I shall simply give my impressions of the results. We have had some of the best results of duodenal feeding in the group of severe cases of gastroptosis with atony, with dilatation of the stomach and delay in emptying, when this was combined with loss of appetite and marked loss of weight. Ordinary cases of malnutrition were not fed in this way. The tube was reserved for the severe and exceptional ones where it was hard to get in enough food by mouth.

In extreme cases it may take a day or two for the tube to pass the pylorus. In 2 cases of this group of 10 the use of the tube was given up, in 1 because the tube remained in the stomach for four or five days, and in 1 because of distress. All the rest did well; gained from four to fifteen pounds during duodenal feeding and in the majority of cases started a permanent gain of twenty to thirty pounds after the duodenal feeding was stopped. This use of the tube is not new but ought to be emphasized, as it proved of great value in difficult cases.

In 10 cases of persistent vomiting we have had some failures but more brilliant results. These were chiefly "medical cases" in nervous women where a reflex or toxic cause had upset the stomach seriously; one was pregnant. I have not used it in obstructive or surgical cases. In 3 cases the tube was vomited and its use stopped; in the rest the result was very satisfactory.

I expected all the patients to vomit the tube at once, and at first it was a great surprise to find that stomachs which did not retain

a few sips of water, did retain the tube and passed it on to the duodenum, and that patients could take with perfect comfort through the tube the same food which a short time before had caused distress and vomiting when taken by mouth. It is possible that an unusual form of treatment may help some patients by mental suggestion. It is certainly encouraging to a nervous woman who has vomited for days to watch the comfortable inflow of a large amount of nutritious food. It is wise to use an unusually long tube in these cases, 100 or 125 cm., to prevent regurgitation into the stomach and vomiting.

It is especially useful if rectal feeding is not retained, and even when rectal feeding was possible the results with the duodenal tube were far better for the reasons given above. I have come to rely upon it when other treatment fails.

In gastric and duodenal ulcer I have been very conservative in using the tube for treatment (possibly too much so). It was only used in cases without stenosis or very marked deformity which had resisted ordinary medical treatment; in short, it was only tried in a small and rather difficult group of ulcers.

The cases were all examined with the *x*-rays to determine the *position and size of the ulcer*. We have used the tube in good-sized ulcers of the duodenum, but only in small ulcers of the stomach for fear of cancer. Dr. Wm. C. McCarthy, of the Mayo Clinic, has told me that the large majority of ulcers of the stomach which were excised and had a crater larger than a dime showed malignant change.

In speaking of results we must remember that the course of gastric and duodenal ulcers is almost always intermittent. Symptoms often disappear with poor treatment or no treatment at all. This makes it very difficult to judge accurately the value of any treatment.

Our results were as follows: In half of the cases, 7 in number, the symptoms were stopped, and recurred in only 1; in the other half, namely 7, the treatment did not succeed and surgery was advised. In 2, small multiple ulcers were found; in 3, small ulcers with considerable adhesions; 2 refused operation. The results with the tube were good considering the difficult class of ulcers

treated; nearly half the group of hard cases were cured of symptoms when other medical treatment had failed.

The method gives the stomach almost complete rest, and at the same time nourishes the patient; where there is much spasm of the pylorus, the method is especially useful; in these cases there may be some delay in the passage of the tube into the duodenum, but this can usually be accomplished with a little patience, or with the help of a few doses of atropin. No real difficulties were met; the average length of feeding was fifteen days. It has also proved valuable in bringing up poor surgical risks to a plane where operation could be performed.

It must be added that men who have had far greater experience, such as Einhorn, Morgan, and Stockton, have used it much more freely in ulcer and report good results; in the saving of time, improved results in difficult cases, and avoidance of surgery. My experience leads me to use it more freely in the future, in a selected group of cases where food by mouth is stopped on account of pain, vomiting or bleeding. If the tube is well borne, it is very much better than rectal feeding; instead of the steady and usually rapid loss of weight and nitrogen in rectal feeding, the nitrogen balance is kept, and the weight usually held or increased.

In two cases of inoperable cancer of the esophagus the tube was successfully used for stomach feeding to relieve starvation and prepare the patient for gastrostomy; there was rapid gain of weight of 16 and 18 pounds respectively. It was difficult to get the tube in; a silk-thread guide was swallowed and a special tube tip was threaded on the guide and gently pushed in with a stylet; in two other such cases it was impossible to get the tube in.

SUMMARY. The clinical use of the duodenal tube has proved its value in a limited field.

A fluoroscopic study of the technic of the introduction of the duodenal tube showed that by placing the fasting patient successively in simple postures, the tube may be introduced into the duodenum within a half-hour in a majority of cases in which organic stenosis is not present. Spasm of the pylorus, atonic and hook-shaped stomachs may delay the tube.

A heavy Gross tube enters the duodenum more rapidly than

a light Einhorn tube. A small tube (No. 8 French) with a heavy tip of at least 100 grains weight (Palefski) is the best of all for diagnostic work. It is not difficult to tell the position of the end of the tube. It is as safe as an ordinary stomach-tube.

In diagnosis, examination of the duodenal contents was most useful in diseases of the pancreas and in cases of chronic jaundice. It is the only method of directly obtaining the secretions of the pancreas and liver, and avoids many of the sources of error in other indirect tests.

There is considerable normal variation in the pancreatic ferments as determined by our present tests; only absence or marked diminution has much value in diagnosis.

Constant marked diminution or absence of trypsin was found (with one exception) only in chronic disease of the pancreas.

Examination of the feces on the Schmidt test diet in some cases was almost equally valuable, and simpler; in others the examination of the duodenal contents was much more valuable.

In diseases of the liver the value of the test in deciding whether the bile passages are completely or partly closed is limited by the lack of a satisfactory test for bile in the duodenal juice.

The duodenal tube is a convenient and comfortable means of obtaining stomach contents; and more reliable than the usual stomach-tube for aspirating small amounts of fasting contents.

In treatment the duodenal tube of Einhorn was very useful in a selected group of cases; it was very useful in cases of persistent vomiting of nervous and toxic type. It was also useful in certain severe cases of malnutrition with anorexia and atonic stomach.

It was useful in a limited group of cases of peptic ulcer. It was only used in cases without organic obstruction and in those which resisted ordinary medical treatment. It was used several times to improve the patient's condition before operation in ulcer, also in two cases of cancer of the esophagus (stomach feeding).

Almost every case was improved by duodenal feeding, and in a considerable number the symptoms stopped.

It is superior to rectal feeding, as patients usually keep their weight or gain, and keep their balance of nitrogen. A reservoir and the Murphy drop method is preferred to a syringe for introducing food.

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A METHOD FOR THE DETERMINATION OF PLASMA AND BLOOD VOLUME

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The Principle of the Method. The principle underlying this method is the introduction directly into the circulation of a non-toxic, slowly absorbable dye which remains in the plasma long enough for thorough mixing and the determination of its concentration in the plasma colorimetrically by comparison with a suitable standard mixture of dye and serum.

Technic. A 1.5 per cent. solution of the dye, vital red, in freshly distilled water is prepared and sterilized by boiling for from five to ten minutes, and then aseptically stoppered in a sterile Ehrlenmeyer flask. This solution is made up as required.

The patient is weighed stripped and the dose determined on a 3 mg. per kilo basis. The skin over the anterior surface of both elbows is cleaned up in the usual manner for venepuncture. Under aseptic technic a small platinum needle (20 gauge), to which is attached a short piece of rubber tubing (from 2 to 3 cm. in length), is inserted into the vein. Ten c.c. of blood are withdrawn into a pipette and emptied into a 50 c.c. centrifuge tube containing just sufficient powdered sodium oxalate to prevent coagulation. The plasma so obtained is used in the preparation of the standard which is described below.[1] The rubber tubing is removed from the needle,

[1] This procedure of taking plasma for mixing the standard in each case was found necessary on account of the great variation in the color of the plasma in different individuals.

the latter being left in the vein, and a 20 c.c. Record syringe containing the exact dose[1] of the dye is attached and its contents injected, after which the needle is withdrawn. Three minutes later a needle is inserted into the vein of the opposite arm. Without impeding the venous return, 10 c.c. of blood are withdrawn immediately by means of a pipette and two to three minutes later 10 c.c. are again withdrawn. The first specimen is placed in a 50 c.c. centrifuge tube, the second in a 15 c.c. graduated centrifuge tube. To each sufficient dry oxalate is added to prevent clotting, and the tubes are capped with rubber to avoid evaporation during centrifugalization. The three tubes are placed in a high-power centrifuge and subjected to 3000 revolutions per minute for twenty minutes.[2] After removal from the centrifuge the relative proportions of erythrocytes and plasma in the graduated tube are noted. Without disturbing the red cells the plasma is carefully pipetted off from each tube and placed in a clean test-tube. We now have three test-tubes, one containing plasma without dye, and the other two containing plasma with dye in an unknown concentration. A suitable dye plasma standard mixture of known dye content must be prepared, and with it tubes two and three are compared.

The standard dye preparation[3] is made as follows: 0.5 c.c. of the solution (7.5 mg. of the dye) used for the injection is brought

[1] The amount injected is 3 mg. per kg. The weight in pounds divided by 11 gives the number of cubic centimeters of a 1.5 per cent. solution to be injected.

[2] To prevent hemolysis all pipettes and centrifuge tubes must be thoroughly washed with normal saline solution and dried before use. It is obvious that the slightest hemolysis will alter the color of the plasma and make accurate colorimeter readings impossible.

[3] Obviously the standard must be sufficiently intense in color to insure the patient's readings falling on the scale. Since the smaller the amount of plasma in relation to the body weight the greater will be the intensity of the dye; a standard must be chosen which will be more intense than the plasma-dye mixture obtained from normal patients having the smallest proportion of plasma in relation to body weight. The standard selected has been prepared on the following basis: The amount of drug injected is placed in the number of cubic centimeters of salt solution corresponding to the number of grams represented by 4 per cent. of the body weight or expressed differently in the amount of salt solution represented by 40 c.c. for every kilo of body weight: this amounts to 0.5 c.c. (7.5 mg.) of the solution injected, to 100 c.c. of 0.8 per cent. NcCl. For example, a patient weighing 70 kilo would be given 210 mg. or 3 mg. per kg. of vital red, which is equal to 14 c.c. of a 1.5 per cent. solution. Four per cent. of 70 kg. is equal to 2.8 kg., and without making a correction for the difference in specific gravity between the blood plasma and water this would amount, roughly, to 2800 c.c. Now, if 210 mg. are dissolved in 2800 c.c. then 7.5 mg. should be dissolved in 100 c.c.

up accurately to 100 c.c. with 0.8 per cent. sodium chloride. This is mixed with the patient's serum and the salt solution in the following proportions: 1 : 1 : 2, yielding a dilution of 1 in 4. With this solution the prism of the calorimeter (Rowntree and Geraghty's modification of the Autenreith-Königsburg apparatus) is filled. This dilution has been found to be well adapted to colorimetric determinations. Each of the specimens two and three of the patient's plasma is diluted with three parts saline and placed in the cup of the colorimeter and read against the above standard.

Calculation of Results. The method described above furnishes volume values for plasma and total blood. When it is desired to express values as percentages of body weight or as fractions of body weight the formula given below can be utilized. Since the specific gravity of the plasma and blood were not ascertained in this study a specific gravity of 1.050 for the whole blood and 1.030 for the plasma has been used.

Formulæ. Plasma volume.

Weight of patient in kg. = W.

Standard prepared so that amount of dye injected is diluted in 40 c.c. for every kg. of body weight.

Reading of standard prepared as directed = 100.

Reading of patient's plasma against standard = R.

The number of c.c. of plasma in patient's body $= \frac{100 \times 40\ W.}{R}$

$= \frac{4000\ W}{R}$

Percentage of body weight.

Plasma volume in c.c. $\times \frac{\text{Sp. Gr. of plasma}}{1000}$ = weight of plasma = X.

$\frac{X \times 100}{W}$ = per cent. of body weight.

c.c. of blood per kg. $= \frac{\text{number of c.c. in body}}{W}$

Total Blood Volume. Let hematocrit reading of the volume occupied by corpuscles = P.

Volume of plasma = 100 − P.

Total blood volume $= \frac{\text{plasma volume} \times 100.}{100 - P}$

Total Blood as Percentage of Body Weight. Total blood volume in c.c. $\times \frac{\text{sp. gr.}}{1000}$ = weight of total blood = Y.

$Y \times \frac{100}{W}$ = per cent. of body weight.

Number of c.c. per kg. = $\frac{\text{number of c.c. in body.}}{W}$

Results. At least 140 determinations of plasma volume have been made on more than 100 individuals. In the earlier work hematocrit studies were not made, so that the values for total blood volumes are considerably fewer.

Normal Values. The results here reported are for normal men, being obtained from patients attending the out-patient department of the genito-urinary clinic for some minor local condition, such as chronic urethritis, chronic prostatitis, or verumontanitis, etc.

Plasma Values. Forty-five determinations were made on thirty-nine patients. The largest (3775 c.c.) and the smallest (2450 c.c.) volumes were encountered in the heaviest (85 kg.) and lightest (47.4 kg.) patients. The mean weight was 61.2 kg. and the mean volume 3125 c.c.; the average weight, 63.3 kg. and the average volume 3050 c.c. (From this it appears that a normal man of 140 pounds has three liters of plasma, or 50 c.c. per kg.) The constancy in the relation of plasma to body weight in health is striking, there being no great extremes. The plasma varied from 42 to 56 c.c. per kg., while the fraction of body weight varied from 1/23 to 1/17, the average being 1/19.4.

Blood Values. The number of determinations of total blood volumes has not been so large. Twenty-one determinations on twenty normal individuals were made, the whole blood values being calculated from the plasma volume and hematocrit findings. The plasma constitutes on the average 56.9 per cent. of the total blood, the extremes being 51 and 62.6 per cent. The largest and smallest volume (6675 c.c. and 4200 c.c.) were obtained in the two patients mentioned above as having the largest and smallest plasma volumes. These patients showed 78.5 and 97 c.c. per kg. respectively. The average blood volume was 5350 c.c. or approximately 85 c.c. per

kg. On a gravimetric basis the blood constituted 8.8 per cent., or 1/11.5 of the body weight. The variations in health were not great, being from 1/13 to 1/10.5 of the body weight.

The details of this study together with the results obtained in various diseases will appear in an early number of the *Archives of Internal Medicine.*

DISCUSSION

Dr. Theodore Janeway: Great interest attaches to the method for determining total blood volume, because it offers an opportunity to prove the existence of a true plethora. It has been a disappointment to find that this condition has not existed in those patients already examined in whom we had anticipated it.

PHYSIOLOGY AND PATHOLOGY OF THE DUODENAL MUCOUS MEMBRANE

By THOMAS R. BROWN, M.D.
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Before discussing the physiology and pathology of the duodenal mucous membrane it is important to call attention to certain factors outside of the duodenum but intimately connected with its function. We will not discuss the methods of study which have given us our knowledge of the conditions obtaining in this most interesting and complex portion of the digestive tube—the study of the stool for ferments, complicated products of digestion and metabolism and occult blood, the relative value of such findings compared to those from the duodenal contents obtained directly through one of the various duodenal tubes, or from aspiration of the stomach after administering oil, the methods of animal experimentation by the use of gastric and duodenal fistulas, by isolating the duodenum, by intravenous administration of extracts of the wall, bacteria, toxins, etc.—but will confine ourselves to a brief discussion of the factors involved in the emptying of the pylorus and the constitution and character of the pancreatic juice and bile. The intimate connection between gastric discharge and the flow of bile, pancreatic and duodenal secretions is, of course, well known. We know that vagus impulses cause the initial psychical gastric juice and also increase pyloric tonus, that the control of the pylorus is fundamentally due to the acid in the gastric contents and that of the first portion of the duodenum, in the former causing opening, in the latter closure, and that the latter seems to be the stronger reflex of the two; we realize that the differential discharge of

different foodstuffs is in the main explicable upon the rapidity with which the acid reaches the pylorus and duodenum, that fats inhibit both secretion and pyloric tonus, that there is also an ileopyloric reflex; that is, when a large column is behind the cecum the pylorus is automatically closed and that tonic action and peristalsis are entirely distinct muscular functions. These facts have been determined by careful observation and experiment; one may show that hydrochloric acid opens the pylorus of the excised stomach; that the appearance of acid near the pylorus closely precedes the discharge; that hastening the acid reaction delays the initial discharge; that acid in the duodenum inhibits the gastric discharge; that absence of the normal alkaline secretion in the duodenum retards gastric discharge, and that it is hastened by destruction of continuity between stomach and duodenum, an important fact as regards gastrojejunostomy. Certain facts are not so easy to explain—the rapid discharge of water and of egg white, the rapid emptying in achylia gastrica, etc. We have shown in dogs the importance of the tonicity of the fluid in this connection, hypertonic fluids leaving the stomach much more slowly than iso- or hypotonic. Certain other questions in the motor sphere are of real interest—the significance of the dilated duodenum so often seen in pathological conditions, and whether it is a gastromesenteric ileus, which seems improbable, or is caused by reflex inhibition from elsewhere, or possibly may be due to a hormone originating in the pancreas, or whether it represents a lack of balance between vagus and sympathetic due to over- or under-production of certain intestinal toxins. It is probable that the reflexes are operated through the myenteric reflex; that reflexes in the gastrointestinal tract always cause contraction above and relaxation below the point of stimulation; that the speed of propagation in the intestine is adapted to the rate of absorption; that as a rule only under abnormal conditions can the food column be clearly seen after it passes the caput duodeni; that any form of duodenal irritation is likely to be associated with pyloric relaxation, and that this is also met with in lesions of the small intestine, in practically all cases of appendicitis and often in mucous colitis and after psychical disturbances. In fact, the control of the pylorus seems to be

regulated by some sensory mechanism in the duodenum, a mechanism closely connected with other portions of the digestive tract, although the exact role played by the local and the central nervous system in this connection has not as yet been definitely determined. As regards the pathological gastric secretion we know that its absence or diminution is associated with a low degree of pyloric tonus, which accounts for the reflux of duodenal contents in achylia gastrica and after fat feeding. The pancreatic secretion is under both psychic and chemical control, the former easily shown in dogs with pancreatic fistula, secretion beginning from one to one and a half minutes after the ingestion of food, and even after the sight or smell of it, and lasting for from ten to thirty minutes. The alkalinity of the juice not only furnishes a medium suitable for the action of its ferments, but also plays a large role in the pyloric reflex. The important ferments of the pancreas, diastase, lipase, and trypsin-zymogen are, according to most investigations, secreted in varying amounts according to the character of the food; other ferments have also been described—a rennin—and a hemolysin—zymogen, a nuclease, and possibly in children a lactase. Bickel has shown that the pancreas is subject to secretory variations analogous to those seen in the stomach. Wohlgemuth has shown the opposing action of the pancreas and the suprarenals, and we the primary stimulating and secondary inhibiting effect of bile upon this secretion. It is conceivable that the pancreatic secretion might be brought about by nervous channels, as Pawlow believes, by the direct action of substances preformed in the foods of the product, of digestion, of a specific hormone. The last is unquestionably the major cause under physiological conditions, and is formed by the conversion of the prosecretin found in the duodenal mucous membrane into secretin by the action of hydrochloric acid, while a similar stimulant action follows the administration of water, fats and soaps, the two former producing a very faint, the latter a fairly strong secretion, possibly due to another secretin—saprokrinin, while the action of fat is probably reflex not hormonic. The pancreas unquestionably is also an important regulator of the motor function of stomach and duodenum. The fact that we have shown that in achylia gastrica there is usually a normal flow

of pancreatic juice shows that under pathological conditions the usual mechanism may be supplanted; whether by reflex stimulation or the development of a new secretin susceptible of function under different stimuli one cannot say.

Probably activated through secretin and also possibly through nervous channels as well, the bile also plays an important part in duodenal digestion, not so much from its ferments as with the possible faint trace of diastase and of a proteolytic enzyme it has none, but by its activating influence upon trypsin, diastase, and especially lipase, and its large role in aiding the absorption of fats by change in the physical as well as the chemical status of the medium, largely through the influence of the bile salts, which diminish surface tension and dissolves fatty acids, soaps, lecithin and cholesterin, these bile salts being probably reabsorbed and then acting as stimulants of hepatic function. While the secretion of bile seems to be continuous its elimination is, according to most observers, largely dependent upon the same mechanism as that of the pancreatic and duodenal secretions—secretin. Pawlow, however, does not believe that this plays a large role here, and has shown that fats and albumoses applied to the duodenal mucous membrane called forth a rich flow of bile. The close connection between duodenum and liver, whatever the channel, possibly nervous, probably chemical, is undoubted.

This brief review of pyloric reflex, gastric and pancreatic secretions and bile will show to what a multiplicity of influences the duodenal mucosa is exposed. In the duodenum the villi are thicker than farther down the small intestine, and it has its own glands, the acinous glands of Brunner as well as the tubular glands of Lieberkühn, situated between the villi and superposed upon adenoid tissue, which are present through the small intestine. There is a slight, constant secretion of mucus from the duodenal membrane, which may become considerable under mechanical or chemical stimulation, and which if long lasting may lead to a chronic catarrh or duodenitis associated with a permanent increase in the mucin-secreting cells. As in the small intestine so in the duodenum secretion and absorption go on together, but it is the former which is of paramount importance. And yet notwithstanding the ingestion

of food and the flow of bile, pancreatic juice and duodenal secretion, all physiologically due in the main to secretin, this as well as the lower portion of the gut is never distended under normal conditions due to rapid peristalsis and quick absorption. It is interesting to remember that in the duodenum under physiological conditions the simultaneous presence of the three juices necessary for a complete duodenal digestion is insured in the main by the same mechanism, although in the intestinal juice there is also probably a new secretin which may cause renewed flow after absorption. On the other hand, direct mechanical stimulation of the duodenal mucous membrane causes a secretion, while there is the possibility of a psychic and reflex secretion as well. The duodenal juice is alkaline, but less so than the pancreatic secretion.

One has but to mention the ferments present in the duodenal secretion or in the wall of the gut to realize the extreme complexity of the chemical and physical processes carried on here. Besides the pro-secretin, not a ferment, of course, but of fundamental importance in the calling forth of ferments, we have erepsin, enterokinase, arginase, nuclease, lipase, maltase, invertase, lactase, possibly a slight trace of diastase from Brunner's glands, a hemolysin, and a glucoside- and a cellulose-splitting ferment. The fact that extracts of the wall are much richer in ferments than the juice itself, notably in the case of erepsin and the inverting ferments for the conversion of di- into monosaccharides, suggests that a considerable part of the ferment action takes place as the substances pass through the wall, the time for which according to Heidenhain is at least several minutes. Of these ferments the most interesting perhaps are erepsin, which is also present in many tissues of the body and which accelerates the digestion of the end-products of peptic action, and the enterokinase, which converts the inactive trypsinogen into active trypsin. In considering the action of enzymes certainly the most helpful view is that ferment and substrate occupy the same relationship as toxin and antitoxin, lysin and antilysin, with its specificity of action due to its haptophore group. Pro-secretin seems to be present in the whole thickness of the mucous membrane, the enterokinase in much greater abundance in the cells covering the villi. While there is no absolute proof of it,

it is probable that the same selective tendencies as regards the character of the food ingested is met with in the duodenal secretion as in the pancreatic flow, with the same possibilities of qualitative and quantitative functional variations, and that in the motor sphere it is probable that atony and spasm may also be met with as purely functional disturbances, as possibly the duodenal dilatation described by Barker and Estes in cases of family hematoporphyrinuria. As elsewhere in the intestinal tract here also diverticula may be found, probably congenital in the second and third portions, either congenital or due to ulcer or widening of the vestibule in the first portion.

As regards the pathology of the duodenum the most interesting questions are: (1) the nature of the peculiar dilatation met with in certain cases with vague symptomatology regarded by some as a gastromesenteric ileus, by others as an expression of sympaticotony, and by still others as due to variations in the hypothetical pancreatic hormone presiding over the tone of the duodenal musculature; (2) the various unsolved problems in connection with duodenal irritation and duodenal ulcer, and (3) the possible excretory function of the duodenum and its relation to high intestinal obstruction.

Duodenal ulcer is probably caused by the direct action of trypsin and other proteolytic ferments, as, for example, those set free from the leukocytes, upon a portion of the mucous membrane. Whether this is due to the absence or diminution of the normal protective antilysins and antienzymes, whether it is brought about by disturbances of the blood supply to the area involved, or whether absorbed cytotoxins play a role it is hard to determine. The greater prevalence of ulcers in the first portion of the duodenum is perhaps due to mechanical causes, perhaps due to the fact that this portion bathed as it is periodically in strong hydrochloric acid is more susceptible to changes, perhaps it is due to pressure upon the bloodvessels by the swollen Brunner's glands. Certainly in most cases duodenal ulcer is due to trophic changes of reflex character, dependent usually on stimuli arising from lesions or toxemias in other portions of the alimentary tract, notably terminal ileum, appendix, and first portion of the large bowel. In fact there seems

to be a nervous mechanism in close relationship with the duodenum to which disturbances in other portions of the tract are referred. In its etiology, however, both local and constitutional factors probably come into play; certainly it is frequently met with in that type of psychoneurotic individual with signs of irritation in various parts of the vegetative nervous apparatus, a condition often spoken of as vagotony, and possibly due, as Eppinger has suggested, to an over-production of vagus-stimulating substances, or perhaps an over-absorption in the large bowel, and a breaking down of the balance normally maintained between vagal and sympathetic stimulation. The fact that induced anemia in animals prevents the healing of artifically-produced ulcers is also of interest. The experiments showing that the intravenous injection of selected strains of the colon bacillus will cause ulceration in rabbits, and especially Rosenow's demonstrations that certain strains of streptococci produce gastric and duodenal ulceration suggest that bacteria may play a role, probably hematogenous and possibly specific. It is certainly of especial interest in connection with the undoubted relation between gastric and duodenal ulcers and various foci of infection, notably infected tonsils, pyorrheal pus pockets, infected gall-bladders, and diseased appendices. One must not forget, however, that certain poisons introduced intravenously are also capable of producing ulceration, and that it is met with in conditions in which infections probably play but a scant role, such as certain cases of polycythemia. In connection with the former the frequency of duodenal ulcer, in which all signs, the alkaline stool, the presence of many gram-positive anaërobes, the increase of the coefficients of Combe and of Amann, suggest the probable over-production of intestinal toxins, should not be forgotten. In the rational treatment of duodenal ulcer all these possible etiological factors must be taken into consideration if one hopes to obtain a cure. In the diagnosis of duodenal ulceration, especially interesting is the attempt of the experts in fluoroscopy and radiography to ascribe to this condition a picture sufficiently definite to warrant a diagnosis. Certainly hyperperistalsis, hypermotility, paradoxical hypermotility, and dilatation of the duodenum are met with surprising frequency in these cases. Unfortunately

certain of these pictures may also be found in simple duodenal irritation, in various lesions of the stomach and of the small intestine, and in many cases of appendicitis. This tendency toward pyloric relaxation, duodenal dilatation, and absence of segmentation contractions is apparently more than enough to counterbalance the inclination toward spasm usually met with in ulceration, and possibly explains the far greater tendency toward spontaneous healing of duodenal as compared to gastric ulcers. Cole's intensive studies of the appearance of the duodenal cap by serial radiography are of especial interest in this connection.

The very stormy symptoms in high intestinal obstruction usually followed by death in a short time have led many to study the pathology of the duodenum from another point of view, that is, the role it plays in this symptom-complex. There are various theories in this connection: (1) that it is of reflex action, which obviously is inadequate; (2) the theory of bacterial origin, also difficult of acceptance because of the relative paucity of microbes in this portion of the digestive tract (and thus this theory, although supported by Brooks and Maury, has been in the main rejected); (3) that the bile and pancreatic juice play a role—improbable, as shown by various animal experiments; (4) that the duodenum is also an secretory organ, and secretes a toxin, the view especially supported by Stone, Bernheim and Whipple, Bunting and Jones concluding that this poison is purely duodenal in origin and comes from Brunner's glands: the former authors from a long and elaborate series of experiments believe that the mucous membrane itself normally secretes a poison; that it is not due to bacterial action; that it bears no relation to disturbances of the blood supply or abnormalities of innervation; that the toxins secreted react in many ways like members of the cholin group, and that the clinical symptoms met with are low blood pressure, subnormal temperature, muscular and nervous weakness, and a weak, rapid pulse, and that a considerable degree of immunity may be produced by a partial obstruction; (5) the view of Hartwell and Hoguet, violently opposed to the preceding, as they believe that the symptoms are due to the sudden loss of water, on the one hand, and on the other, to a toxin produced by injury to the mucous membrane and the blood-

vessels, and if these are intact no harm results. Thus we will see what very complex processes are carried on in these few inches of gut in contact with this small amount of mucous membrane—the effect of variations in the gastric and pancreatic secretions and in the bile, and various stimuli from the motor sphere all standing in intimate relationship to the problems presented.

From the foregoing brief review of the subject we may see how much progress has been made in solving many of the problems connected with the physiology and pathology of the duodenal mucous membrane. Certain conclusions stand out very prominently: (1) the peculiarly intense correlation and connection between the various portions of the gastro-intestinal tract, and our absolute inability to consider any portion as a separate organ; (2) the presence of various mechanisms to call into play the processes of digestion, one as a rule predominating under physiological conditions, the others possibly only of importance when the normal stimulation is lessened or completely inhibited by lack of proper stimuli; (3) the wonderful field for research still presented by this very complex portion of the digestive tract in solving problems of prime importance (to the physiologist and the chemist as well as to the clinician and surgeon)—the cause of duodenal ulcer, its relation to inflammatory conditions elsewhere, the possible specificity of bacteria in its causation, and the complete solution of the problems associated with high intestinal obstruction.

CHRONIC DUODENAL ULCER

By WILLIAM J. MAYO, M.D.
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(By Invitation)

In the presidential address delivered before the American Surgical Association in 1900, Dr. Robert F. Weir[1] called attention to the surgical possibilities of ulcer of the duodenum. In his masterly presentation of the subject he dealt chiefly with the acute cases, especially those in which perforation had taken place. Within the following year the condition was recognized in examining patients in our clinic and several cases were operated on. The previous history in each case was so distinctive as to attract attention at once. Before the perforation occurred, the patients suffered from intermittent digestive disturbances followed by intervals, sometimes of great length, in which they were fairly well. The symptoms complained of were characteristic—hyperacidity, hypersecretion, hunger pain, food relief and, in the later stages, the phenomena which accompany obstruction.

These various findings were most interesting and led promptly to a more careful examination of similar cases which we had been operating on for so-called pyloric obstruction, supposedly due to ulcers of gastric origin. The investigation showed that a high percentage of the ulcers believed to be pyloric were in reality in the first portion of the duodenum.

In 1904 I reported to the American Surgical Association 58 cases of undoubted duodenal ulcer which C. H. Mayo and I had operated on.[2] Even at that time we had no conception of the frequency with which duodenal ulcer occurred. This is shown by

a comparison of statistics of cases operated on in our clinic as noted at subsequent dates: In 1904 the relation of gastric ulcer to ulcer of the duodenum was: gastric, 73 per cent.; duodenal, 27 per cent.; in 1907: gastric, 52 per cent.; duodenal, 48 per cent.; in 1910: gastric, 35 per cent.; duodenal, 65 per cent.; in 1914: gastric, 27 per cent.; duodenal, 73 per cent.;

Our work during this early period was greatly stimulated by the splendid contributions of Robson and Moynihan, whose observations and results agreed with those in our clinic. The fact that surgeons working simultaneously in different countries should come to the same conclusion seemed very significant.

The idea that duodenal ulcer was more frequent than gastric ulcer was slowly evolved. Surgeons investigating conditions at the operating table were more readily convinced than physicians working along the lines of specialized gastro-enterology. A prominent specialist in gastro-intestinal diseases once asked, "How is it possible that you, a general surgeon, see so many of these cases, while I, who am devoting all my time to this work, see so few?" I could only answer, "The thickness of the abdominal wall prevents you from seeing them."

Postmortem statistics have been and are still quoted in opposition to the view that duodenal ulcer is a frequent condition. For example, the statistics of Rokitansky,[3] master pathologist, were published in 1839. Brinton,[4] whose statistics are so readily quoted on every occasion, published his work in 1857. These did not represent Brinton's personal observations, but what he had gleaned from postmortem records obtained from diverse sources previous to that time and did not necessarily represent facts, but their interpretation in the light of the time when the statistics were compiled. The statistical method of settling such questions is none too good at best, and when the statistics are from fifty to seventy-five years old they can hardly be accepted as representing modern thought on the subject of gastric and duodenal ulcers.

The methods of clinical study have been even more chaotic. For example, compare the clinical diagnoses of gastric ulcer upon admission to the hospital with the autopsy findings ten years ago. Take three hospitals in Philadelphia: University Hospital, clinical

diagnosis of gastric ulcer, 0.48 per cent.; Pennsylvania Hospital, clinical diagnosis, 0.13 per cent.; Blockley Hospital, as the result of autopsy findings, giving 1.42 per cent. of gastric ulcers (Francine[5]). In other words, in two hospitals of exactly the same character in the same city ulcer was diagnosed clinically nearly four times as often in one as in the other, while both fall short of the actual postmortem findings in the third hospital from three to eleven times. Duodenal ulcer was seldom mentioned as a clinical or autopsy finding. Francine says: "We cannot base accurate or conservative conclusions on data obtained from clinical observation."

Without going further into the question of the relative frequency of gastric and duodenal ulcers, it may easily be seen that the clinical and postmortem demonstration of peptic ulcers has been, to say the least, misleading. The Germans, who were slow to investigate duodenal ulcer, were the greatest comfort to those who did not believe that duodenal ulcer occurred with any degree of frequency. A celebrated German surgeon said in explanation, "We relied too much on the supposed knowledge of the gastrointestinal specialist; he was so positive that we really thought he knew." The change in opinion in Germany within the last two years has been very remarkable, and is best demonstrated by Kümmel's[6] statistics of the Eppendorf Hospital. Quoting from his recent paper: "It is not uninteresting for me to explain to you how in the relatively short time, especially within the last few years, the number of duodenal ulcers has increased among us and how a notable gain in the *actual objective material* in our *pathologic institutes has been brought to light by Fraenkel.*"

TABLE SHOWING THE RELATIVE NUMBERS OF GASTRIC AND DUODENAL ULCERS (KUMMEL)

From 1897 to end of 1911,	191	gastric ulcers to	16	duodenal.	
1912,	10	"	"	7	"
1913,	11	"	"	30	"
First three months 1914,	no	"	"	12	"

Of equal significance is the work of Schrijver,[7] of Amsterdam, who shows the same striking increase in the recognition of duodenal

ulcer. Those experiences can be multiplied from all the advanced European clinics. The clinical frequency of duodenal ulcer has been demonstrated by exact methods under the sense of sight in the operating room.

Wilkie,[8] of the Royal Infirmary of Edinburgh, has found 41 (9.9 per cent.) duodenal ulcers in 490 postmortems. In only 6 cases had antemortem diagnoses been made; these had been operated on. Wilkie quotes Gruber that 75 per cent. of duodenal ulcers found after death have not been diagnosed during life.

The experimental production of gastric and duodenal ulcers as yet appears to have little bearing on chronic callous ulcer. There is a type of acute ulcer probably toxic in origin which gives rise to sudden severe symptoms often followed by perforation or hemorrhage. These patients left untreated either die or completely recover within a few weeks. The ulcers are multiple; there is no callus and several ulcers may perforate simultaneously. So far as I have been able to observe, experimental ulcers belong to this class and are of very little value in determining the character and position of the chronic callous ulcer of the duodenum. The latter are usually single, seldom begin with an acute attack, and, as a rule, the earlier symptoms are less severe than the later ones.

It is interesting to speculate as to what diagnoses were made in the cases of duodenal ulcer prior to our present knowledge. It is altogether probable that a large percentage of chronic duodenal ulcers were not diagnosed at all. Some were believed to be gastric ulcers. A high percentage of acute perforations were believed to be acute appendicitis, since the fluids quickly gravitate into the right iliac fossa and the appendix as well as the surface of the intestines early shows marked evidences of peritonitis. Ten years ago it was taught that an appendix apparently normal in its mucosa, under certain conditions, permitted bacteria to pass into the peritoneal cavity, causing septic peritonitis. The mistake was often not discovered even at operation, and the death of the patient came after extensive peritoneal involvement had obscured the site of perforation in the duodenum sufficiently to prevent recognition. The experience of the Massachusetts General Hospital, as reported by Codman,[9] is instructive in this respect.

I shall not go into the question of the etiology of duodenal ulcer. It is quite evident that the same causes which produce gastric ulcer produce duodenal ulcer. The thrombosis and embolism theory, the nerve theory, the bacterial theory, the mechanical theory, and the erosion theory all have their advocates. The latest recruit to the infection theory is Rosenow,[10] whose splendid investigation as to the relation of the streptococci in the terminal capillaries of the mucosa to ulcer of the stomach and duodenum is most illuminating. This theory is borne out by the edematous, inflammatory character of the ulcerous duodenum found when operating during an exacerbation of the symptoms, and further by the fact that following acute perforation of an ulcer, if the patient is so fortunate as to recover, the ulcer heals as though some harmful agent had been extruded. If later other symptoms are manifested, they are due to the obstruction or deformity which follows in the wake of the ulcer.

One possible source of injury to the mucosa of the lesser curvature of the stomach and duodenum, which may have some bearing on the etiology of peptic ulcer and also to cancer of the stomach, is hot drinks. Solid food is masticated in the mouth and then passes into the fundus of the stomach where it is retained during the early period of gastric digestion. If the food is very hot, it is more or less cooled in the act of mastication, but drinks are taken into the stomach much hotter than can be borne in the mouth. Anyone taking the trouble to experiment will probably find they have been in the habit of swallowing fluids much too hot to be held in the mouth comfortably. The stomach and duodenum give no immediate indication that the fluid is too hot. These hot fluids are carried rapidly along the lesser curvature into the duodenum to the exact situation in which the majority of ulcers are found, possibly removing the protective mucus which prevents auto-digestion and which may result in chronic irritation. Extreme cold drinks may have the same effect. The experiments of Jefferson[11] as to the canalis gastricus have shown that liquids, when taken in considerable quantity, pass rapidly along the lesser curvature and into the duodenum without mixing with the food mass in the fundus.

The pyloric veins are most valuable in differentiating gastric from duodenal ulcer. A short, stumpy vein comes out from above and another from below the pylorus, sometimes sending a small branch across the top of the pylorus (Fig. 1). These veins are

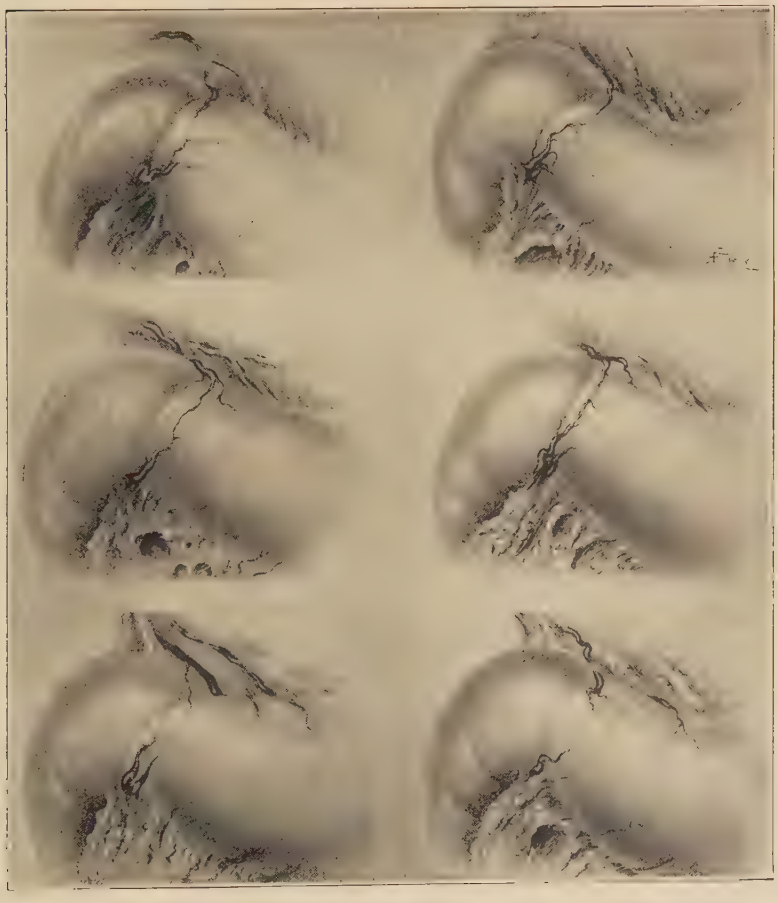

Fig. 1.—Types of pyloric vessels in relation to the location of the pylorus.

quite unlike the vessels of other situations of the stomach and when their peculiarities have once caught the eye they serve readily to locate the pyloric ring. Gastric ulcer in the pyloric end of the stomach is not often mistaken for duodenal ulcer, but for cancer,

as in this situation a tumor usually forms in connection with the ulcer as the result of muscular hypertrophy and edema.

The large majority of ulcers of the duodenum are located in the first one and one-half inches, more often on the anterior wall. A number begin just below the pylorus and at first glance they appear to involve the pyloric ring, especially when extensive and obstructive, but careful examination will show that they are duodenal. The deeper, larger ulcers and those which bleed excessively are more often situated on the posterior wall, the callus sometimes extending into the head of the pancreas. Such ulcers may be concealed from view underneath the pyloric ring, but seldom involve the gastric mucosa. When an ulcer is situated on the posterior wall, a superficial contact ulcer will usually be found opposite on the anterior wall. The mucosa of the duodenum is thin, smooth and granular, and chronic duodenal ulcers may not therefore have the characteristics we have learned to expect from experience with gastric ulcers. I have excised a number of duodenal ulcers in which there was considerable scar tissue in the submucosa and muscularis and marked evidence of localized peritonitis; yet the actual ulcer was a mere slit or dimple surrounded by an eroded, discolored, "moth-eaten" patch of mucosa. This is the type of ulcer which occurs on the anterior wall unless there is a corn-like thickening over the top of the ulcer, in which case it will have the size, depth and callus characteristic of gastric ulcer.

Ulcers may exist in the duodenum at any point above the opening of the common duct or even down as low as the opening. I have observed three cases marked by repeated hemorrhage in which the ulcer involved the papilla of the common duct on its superior surface.

A high percentage of duodenal ulcers perforate the mucosa and muscularis to the peritoneal coat. These are classified as chronic perforations; complete perforation having been prevented by thickening of the peritoneum or adhesions to the gall-bladder, omenta, suspensory ligament of the liver, etc. Many times an acute perforation actually takes place with the recovery of the patient, since the opening may be small, allowing but little fluid to escape and that fairly sterile. In such cases patients have a

localized peritonitis with extreme pain lasting for several days and then make a spontaneous recovery. I have explored a number of such cases during an attack of acute localized peritonitis and have discovered the duodenal opening which had been spontaneously closed by adhesions. Occasionally absorption of the escaping products is incomplete and a phlegmon, usually underneath the liver, forms which can be opened and drained. If this is done gently the original source of leakage in the duodenum will probably not be reopened.

The symptomatology of duodenal ulcer is so well known that in the typical cases failure of diagnosis should not occur. The hunger pain and food relief, hyperacidity and hypersecretion and, in the later stage, obstructive phenomena, leave little doubt as to the character of the lesion. Failure in differential diagnosis[9] may be due to accompanying diseases of the gall-bladder and appendix, etc., which occur in about 16 per cent. In our experience, actual hemorrhage takes place in somewhat less than 25 per cent. of the cases, but if one is satisfied to ask the patient questions and accept doubtful evidence as to black stools, etc., this percentage can be increased to as much as 70 per cent. We have not found occult blood a reliable symptom and do not attach a great deal of importance to it. I say this with some reluctance since many diagnosticians for whom I have the highest respect believe that it is a diagnostic sign of very great importance.

The Rœntgen-ray has been a very important and increasingly valuable means of diagnosis. By this means, when taken in conjunction with the clinical history, a diagnosis can be made in approximately 95 per cent. of cases.

The physical examination, including the use of the stomach tube, is important as evidencing hypersecretion and food retention, tumor, visible peristalsis, etc. Laboratory diagnosis, that is, microscopic and chemical examination of gastric contents, has some value, but is largely of a corroborative nature and has been very greatly overestimated. Dividing into four groups the means of diagnosis, the history is of first importance, the Roentgen-ray second, the physical examinations (stomach-tube findings, etc.) third, and the purely laboratory findings a poor fourth.

One of the most curious phenomena connected with duodenal ulcer is its intermittency. The disease usually begins in young males (83 males to 17 females); after a period of some weeks of symptoms there is a cessation more or less complete and the patient goes for months without any knowledge of his ailment. Then the symptoms recur and after a time the usual remission takes place. This may go on for years, until finally obstruction supervenes and the symptoms become more or less constant, although the gastric muscles may by hypertrophy become competent to overcome considerable obstruction, in this respect acting quite like the heart in valvular disease—periods of competency followed by periods of incompetency.

A study of the history of the natural course of chronic duodenal ulcer makes the prospects of permanent cure by medical means open to question. I have seen a number of so-called "medical cures," and have not been able to determine that there was any material difference between them and the spontaneous remissions. The ulcer, as far as Roentgen-ray evidence is concerned, shows no physical change in the period of improvement. In operating during this period no sign of healing is found. By means of alkalies, restricted diet, frequent feeding, largely milk and cream, whereby chemical corrosions are controlled, patients with chronic duodenal ulcers are relieved; a remission of the symptoms being secured and maintained for an indefinite length of time. But such patients cannot be looked upon as cured unless they can go back, without a recurrence of trouble, to the regular diet of the grade and character obtainable by the average man. As a matter of fact, relapse usually takes place under such circumstances and the dangers of perforation and hemorrhage are ever present.

Other things being equal, after failure of reasonable medical treatment, patients with unhealed chronic duodenal ulcer should be considered surgically. To evade operation in the unhealed case is, I believe, a risk not commensurate with the value received from operative interference. No class of patients gives better results following surgical intervention.

A recurrence of symptoms after operation is most often due to defective surgical technic and usually a gastrojejunal-stitch ulcer,

caused by the use of continuous silk or linen threads. Such sutures may hang, causing ulceration and trouble for months or years. The stitch ulcer produces the same symptoms as the original ulcer: hunger-pain, food-relief, hypersecretion, and hyperacidity. I have reason to believe that many of the poor results

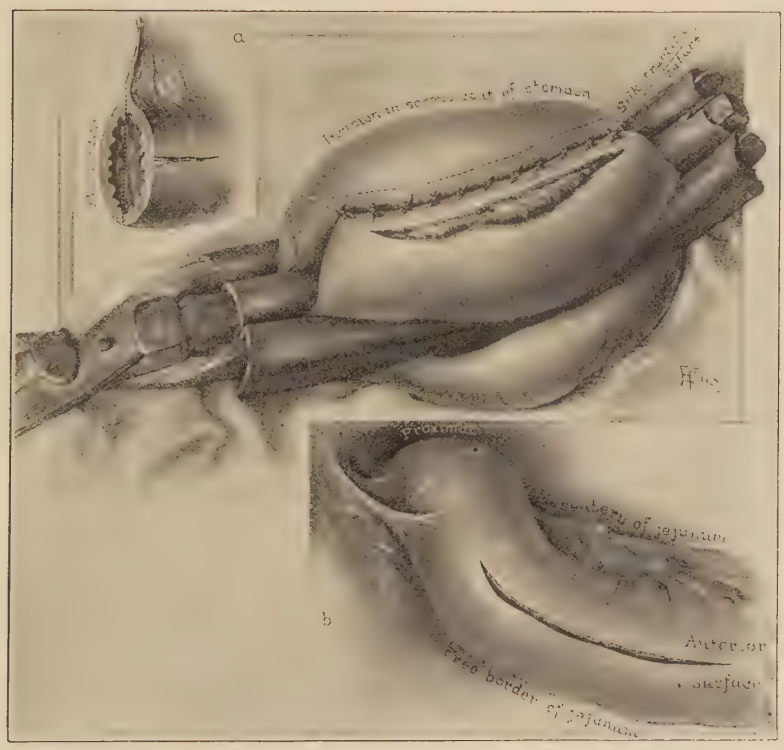

FIG. 2.—Interrupted seromuscular sutures, posterior row, in place. Peritoneal and muscular coats of jejunum incised to mucosa. Dotted line on stomach indicates line of incision. *a*, line of incision in jejunum, not opposite mesentery but on the upper left side. *b*, line of incision in jejunum.

following gastro-enterostomy are the sequelæ of sutures which have finally passed out.

The clinical course of stitch ulcers is quite typical. The patient is operated on for chronic duodenal ulcer and gastrojejunostomy is done. He is relieved and for from three to six months feels fairly well; he then begins to develop the former symptoms and it is

supposed that the original ulcer has recurred. In the course of some weeks or months, about the time the suture finally separates, gradual improvement takes place.

Recently a large number of articles have appeared dealing with the necessity of closure of the pylorus to prevent food from passing down into the ulcerated area. The evidence as to the necessity

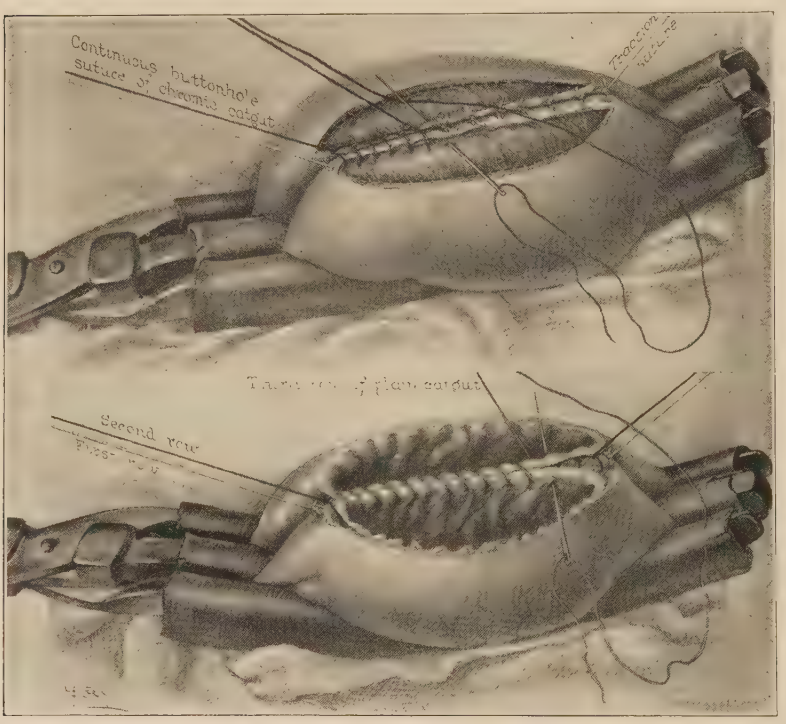

Fig. 3.—Upper figure shows through and through catgut suture of posterior wall before opening the mucosa. Dotted line shows where mucosa is divided. Lower figure shows mucosa flaps stitched across with catgut suture.

of this procedure is not clear. Stitch ulcers and improperly selected patients are responsible for the recurrence of the symptoms in most instances. We have not found that the patients in whom the pylorus was blocked have in any way had results superior to those in whom it was not blocked following simple gastro-enterostomy. If perforation is impending I think it wise to block the pylorus and

cover the ulcer, if there have been hemorrhages this should be done and the vessels in the vicinity of the ulcer carefully tied. But there is no evidence that the routine blockage of the pylorus is advisable or necessary, and if it cannot be done without additional risk, I think perhaps it had better be left undone.

The enthusiastic operator who has made gastro-enterostomies because of symptoms or from suppositious ulcers which he believed

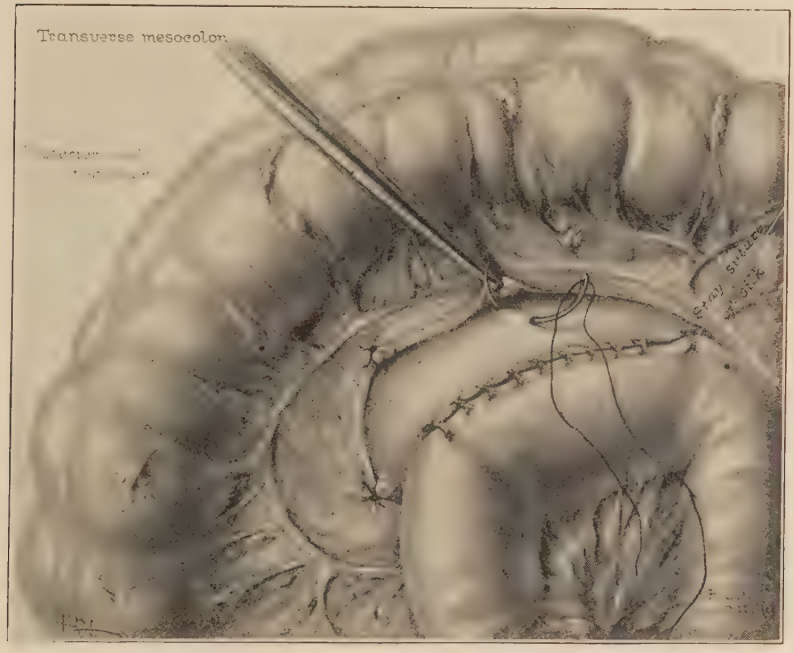

FIG. 4.—Stay suture distal to the anastomosis and suture of margin of the opening in mesocolon to stomach. Note that stomach hangs below transverse mesocolon, making a funnel.

he could see or feel, has greatly harmed gastric and duodenal surgery. In our clinic more than 100 unnecessary gastro-enterostomies have been cut off because of secondary complication such as chronic bile regurgitation, etc. Fourteen of these were our own cases operated on in the early period when it was not understood that a patient should not be operated on unless the ulcer could be actually demonstrated. At the time of these secondary operations

careful search did not reveal evidence that ulcer of the stomach or duodenum had ever existed. Now that blockage of the pylorus has become popular, an alibi is established in advance, inasmuch as the scar made by the ultimate passage of the suture into the gastro-intestinal lumen creates a reasonable doubt as to whether the scar is due to healed ulcer or to the thread. In other words, pyloric blockage often establishes false testimony.

In the large majority of cases gastro-enterostomy is the ideal operation for duodenal ulcer with or without infolding the ulcer. (Figs. 2, 3, and 4.) In selected cases, excision of the ulcer in conjunction with the gastroduodenostomy of Finney is the operation of choice. In those rare cases in which true jejunal ulcer forms following gastro-enterostomy, the jejunal ulcer should be excised, the stomach and jejunal openings closed and the Finney operation done after cutting off the gastro-enterostomy. Following surgical intervention, the patient should be under good medical advice until permanent cure is assured.

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GASTRIC AND DUODENAL ULCER

MEDICAL CURE BY AN EFFICIENT REMOVAL OF GASTRIC JUICE CORROSION

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Favored by unusual clinical facilities, I have gradually evolved and established in practice a method of treating gastric and duodenal ulcers. The method is based on well-recognized principles underlying the healing of ulcer. Old and established facts of physiology are largely utilized. The results of treatment are far beyond early expectations.

The treatment consists essentially in accurately protecting the ulcer from gastric juice corrosion until healing of the ulcer takes place.

After an experience of twelve years in applying tbe principle involved in the treatment, I am convinced that the vast majority of cases of gastric, and more particularly duodenal, ulcer now treated surgically, and with indications commonly accepted as justifiable, can be readily and more quickly cured by the management advocated.

As I understand the ulcer problem, the principles involved in treatment are centred about these important and fundamental questions:

1. What are the causes of peptic ulcer?
2. What retards or prevents the healing of peptic ulcer?
3. What can we as physicians and surgeons do to promote the development of granulation tissue essential to the healing and final cicatrization of peptic ulcer?

For half a century it has been recognized that a peptic ulcer develops in approximately the following manner: A circumscribed area of the mucous membrane or wall of the stomach or adjacent duodenum, through malnutrition or necrosis, loses its normal resistance to the peptic action of the gastric juice and becomes digested. The resulting defect is an ulcer.

The recent work of Dr. E. C. Rosenow renders it probable that hematogenous bacterial (streptococcus) invasion is the most common factor in the production of the local malnutrition and necrosis. Undoubtedly, local defects of malnutrition and necrosis from whatever cause would practically always undergo rapid repair, without serious clinical symptoms, in the absence of gastric juice corrosion.

All present knowledge tends to substantiate the belief that has existed for many years, namely, that an ulcer of the stomach or duodenum would heal approximately as rapidly as an ulcer located elsewhere in the body, if its granulating surfaces were not subjected to the degestive action of the gastric juice.

The digestive action of the gastric juice is due to the solvent action of pepsin on albuminous substances that have been properly permeated by hydrochloric acid. Pepsin is practically inert in alkaline and neutral mediums. It acts slightly in the presence of a combined acid medium, but combined acids are incapable of preparing albumens properly for the action of pepsin. A free acid, such as hydrochloric acid, is required to permeate the albumen and prepare it for the full action of the peptic ferment. Pepsin exerts no appreciable solvent or digestive action on the raw and exposed surfaces of a gastric or duodenal ulcer in the absence of free hydrochloric acid.

The principle involved in the treatment advocated consists essentially in efficiently shielding the ulcer from the corrosive effect of the gastric juice. This is accomplished by maintaining an accurate neutralization of all free hydrochloric acid, thus rendering the digestive action of the gastric juice inert from 7 A.M. until about 10.30 P.M., or during the entire time that food and the accompanying secretion are present in the stomach. In addition, it is accurately determined whether an excessive night secretion is present. If so, this is removed each night until the irritability of the gastric glands

has subsided. This applies almost entirely to cases of duodenal and pyloric ulcer that have been associated with stagnation of food and secretion for one or two months, and longer. Such cases almost invariably are attended by a more or less copious continued secretion during the night, which should be removed by aspiration two or three times each night, if necessary. Usually after three or four days of accurate control of free acidity the excessive night secretion disappears. Subsequently the normal quantity (about 10 c.c.) of gastric juice present in the stomach during the night is left undisturbed.

The neutralization of hydrochloric acid is accomplished by frequent feedings and the use of alkalies in carefully regulated but adequate quantities. Experience in applying the method to all types of individuals under widely varying conditions has abundantly demonstrated that the corrosive or digestive action of the gastric juice can be thus practically annulled until healing of the ulcer is accomplished. The conditions for the healing of peptic ulcer thus obtained are rendered as ideal as they can be made to be in the light of our present knowledge and understanding.

It will be impossible to give the details of the management in this paper. Briefly stated, the patient remains in bed for from three to four weeks. Unless some serious complication is present, some or all of his regular work may be done at the end of four or five weeks. A wide variety of soft and palatable foods may be given. The following plan of diet has been found most adaptable: Three ounces of a mixture of equal parts milk and cream are given every hour from 7 A.M. until 7 P.M. After two or three days soft eggs and well-cooked cereals are gradually added, until at the end of about ten days the patient is receiving approximately the following nourishment: three ounces of the milk and cream mixture every hour from 7 A.M. until 7 P.M. In addition, three soft eggs, one at a time, and nine ounces of a cereal, three ounces at one feeding, may be given each day. The cereal is measured after it is prepared.

Cream soups of various kinds, vegetable purées and other soft foods, may be substituted now and then, as desired. The total bulk at any one feeding while food is taken every hour should not exceed six ounces. Many of the feedings will not equal that

quantity. The patient should be weighed. If desired, a sufficient quantity of food may be given to cause a gain of two or three pounds each week.

A large variety of soft and palatable foods may be used, such as jellies, marmalades, custards, creams, etc. The basis of the diet, however, should be milk, cream, eggs, cereals and vegetable purées. Lean meat is not given during the period of accurate observation, since it interferes with the tests for occult blood in the stool and aspirated stomach contents.

The acidity is more easily controlled by feeding every hour and giving the alkalies midway between feedings. The acidity may, however, be controlled by feeding every two, three, and four hours. I have maintained complete control of the free hydrochloric acidity in several cases by feeding three times daily. In most cases, however, the plan of feeding every hour is best.[1]

It is only fair to state that the views expressed and the methods described[1] in 1911 were as radical as I then dared publish in a handbook for the use of practitioners. Since that time numerous slight modifications of procedure, some of which were then on trial and others of later development, have become thoroughly established in my practice.

The uncomfortable preliminary starvation period serves no purpose when the acidity is controlled and has, therefore, been entirely abandoned. Slightly larger doses of alkalies than were then advised were then being regularly employed. The practice of maintaining an absolutely accurate control of the free hydrochloric acidity during the entire time that food and the accompanying secretion are present in the stomach has become thoroughly established. This requires the administration of varying quantities of alkalies, corresponding to individual cases. Also, in addition to giving an alkaline powder midway between feedings, the powders are continued every half hour after the last feeding, until 10 P.M. In all cases of pyloric obstruction from duodenal and pyloric ulcer it has been found advisable to empty the stomach of

[1] Further details relative to management may be found in my articles on Treatment of Gastric Ulcer, Pyloric Obstruction, etc., published in 1911 in Volume III, Handbook of Practical Treatment, edited by Musser and Kelly.

all remaining food and secretion at about 10.30 P.M., thus removing the stimulus to an excessive night secretion. In most cases a short time after treatment is begun the stomach will be found empty at that time. The management of excessive night secretion has already been described.

Cases of stomach ulcer unassociated with stagnation of food and secretion are usually controlled by feeding every hour and giving a powder containing 10 grains each of heavy calcined magnesia and sodium bicarbonate, alternating with a powder containing 10 grains of bismuth subcarbonate and 20 or 30 grains of sodium bicarbonate, midway between feedings. Cases of pyloric and duodenal ulcer that have been associated with stagnation of food and secretion longer than two months almost invariably require larger quantities of alkalies.

Heavy calcined magnesia has approximately four times the neutralizing power of sodium bicarbonate. Since its neutralizing effect is prolonged compared with that of sodium bicarbonate, and for other reasons, calcined magnesia should be used between as many feedings as possible. An uncomfortable diarrhea usually prevents its exclusive use as a neutralizer. Other stable alkalies similar in action to calcined magnesia are being carefully tested.

In a few cases of duodenal ulcer with high-grade obstruction it has required the equivalent of 100 grains of sodium bicarbonate every hour, midway between feedings, and three doses with intervals of one-half hour after the last feeding, at 7 or 8 P.M., to neutralize all the free hydrochloric acidity.

The average length of time that a patient with peptic ulcer should be under the accurate control and observation of the physician is about four weeks. During this period, if observations have been carefully and intelligently conducted, the finer points essential to a complete diagnosis of peptic ulcer, including such conditions and complications that may attend the ulcer, will have been determined, and the patient will have learned how to manage himself accurately. Thus the gratifying results to be obtained by the management advocated are secured.

It has been my experience that in the management of no other serious disease is it so easily possible to obtain the intelligent co-

operation of all classes of patients. The reasons are probably of this nature: The things required of the patient during the after-management are straightforward and relatively simple; the sufferings of the patient before treatment have often been so severe that he usually requires no further stimulus to do his part. Fortunately, the most accurate coöperation is usually secured from patients who have long suffered from the obstructive types of duodenal or pyloric ulcer.

The non-obstructive type of gastric ulcer requires relatively little attention to details compared with obstructive type of duodenal and pyloric ulcer. The dosage of alkali required to control the acidity is smaller, and it is seldom, if ever, necessary to remove the remaining food and secretion at bedtime.

Ideal conditions for the healing of peptic ulcer are maintained when the aspirated stomach contents show absence of free hydrochloric acid during the entire time that food and the accompanying secretion are present in the stomach, and all excessive night secretion is controlled.

Experience has shown that when the free acidity is found controlled late in the afternoon and just previous to taking the powders or feedings, the acidity is likely to be controlled at all other times during the feeding hours.

It is not difficult to determine the amount of alkali required between feedings to control accurately all free acidity. If not controlled the first few days by giving the usual amount, then the dose is gradually increased until the acidity is regularly found controlled.

It should be understood that the presence of free hydrochloric acid now and then for a few minutes each day does not seriously interfere with the healing of the ulcer. Such short periods during which corrosion of the ulcer may be possible are as nothing compared with the duration of corrosion to which duodenal and pyloric ulcers are subjected after gastro-enterostomy. In the ordinary surgical treatment of these conditions such ulcers are subjected to the corrosive action of the gastric juice during the whole period of normal stomach digestion, which occupies many hours each day. The majority of pyloric and duodenal ulcers treated by gastro-enterostomy show few symptoms after the operation, and such ulcers

probably usually heal in the course of time, the same as the majority of the non-obstructive type of gastric ulcers usually heal without treatment. In either case, however, the conditions for healing are far from ideal.

As will be more clearly stated later, the symptoms of pyloric and duodenal ulcer after gastro-enterostomy and the symptoms of the usual non-obstructive type of gastric ulcer without treatment are approximately the same. Other things being equal, the conditions for healing are approximately the same. Both are subjected to the same duration of gastric juice corrosion. The very great tendency for peptic ulcer to heal, if the hindrance to healing is removed to only a moderate degree, is responsible for the recoveries that occur when gastro-enterostomy is performed for an ulcer located at the outlet of the stomach, causing stagnation of food and secretion.

While the symptoms may be controlled and healing accomplished in the majority of all cases of uncomplicated peptic ulcer by applying the usual or Leube type of medical management; while operative procedure successfully performed, such as gastro-enterostomy and pyloroplastic operations, may be infinitely superior to the Leube and other types of medical management in general use when applied to cases of pyloric obstruction, all types of medical and surgical treatment now in common use accomplish relatively little toward protecting the ulcer from gastric juice corrosion when compred with what may be easily, comfortably, and safely accomplished by applying the accurate medical management which I have established and advocated.

In order that it may be known that the statements made in this paper are based on adequate clinical evidence, I feel justified in saying that at the Presbyterian Hospital I have under my medical management from 25 to 30 and more private cases of peptic ulcer at all times. Fully 70 per cent. of these cases are of the duodenal or pyloric type, presenting abnormal retention of food and secretion, varying from the slightest to the highest grades. The results obtained by such management are almost beyond belief.

Pyloric obstruction due to spasm of the pylorus, resulting in the retention of food and secretion from one meal to the next during

the daytime, and until 3 or 4 o'clock in the morning, and even until the next morning at breakfast-time, disappears at once under the influence of such management.

Pyloric obstruction, even of the highest grade, and of long duration, as evidenced by the presence of vigorous peristaltic waves, showing through the abdominal wall, history of vomiting food eaten the day before for many months, the aspiration of food eaten twelve or more hours before, and the presence of abundant sarcinæ, often rapidly disappears, so that at the end of ten days' or two weeks' management, seven hours after the largest and coarsest kind of a motor meal is given the stomach is found empty.

As unbelievable as it may seem, cases of duodenal ulcer recurrent for years, that have finally developed a high-grade pyloric obstruction due to actual anatomic narrowing from indurated, infiltrated and edematous tissue, have yielded completely to the management.

The explanation for such astonishing results is probably as follows: The active more or less annular ulcer at the pyloric or duodenal outlet is embedded in edematous tissue infiltrated with round cells and other products of inflammation of varying grades. Under the management advocated, the greatest hindrance to healing having been removed, healing and cicatrization of the ulcer begin more or less rapidly, the round cells and other exudative products disappear, the infiltrated tissue grows thinner in all directions, and when healing of the ulcer takes place, notwithstanding the tendency of scar tissue to contract, the opening through the pylorus or duodenum becomes gradually larger instead of smaller. Whatever the explanation, I have accumulated indisputable evidence that the size of the opening through the tissue that is causing the obstruction gradually becomes larger. Recorded observations of such cases now extend over a period of eight years. The early cases of pyloric obstruction due to actual tissue narrowing observed were treated thus medically instead of surgically, because other diseased conditions were present, rendering surgical intervention unusually hazardous.

As a result of the encouraging outcome in these cases, during the past four years, cases have been purposely selected for such investigative work. The results were so uniformly good that within

the past two years a constantly increasing number of cases of that type have been treated thus by medical management, without being subjected to surgical operation. Up to the present time our experience is that none has failed to show that the obstruction yields in the course of a few weeks' or months' management, during all of which time, except the first four or five weeks, the patient is on his own responsibility, so far as treatment is concerned, and doing practically all his regular work.

Roentgen-ray studies of cases of pyloric obstruction after gastro-enterostomy have convinced me that very much the same thing occurs after gastro-enterostomy. As the ulcer heals, the food passes more and more through the pylorus. Since the conditions for healing of a pyloric or duodenal ulcer after gastro-enterostomy are not so favorable as they are under accurate medical management, as advocated, the opening up of the obstruction does not take place as rapidly, and perhaps not as completely.

In the light of all present knowledge, the development of granulation tissue leading to the healing and final cicatrization of peptic ulcer is promoted by a given type of medical or surgical treatment directly proportionate to the influence exerted by that treatment on the duration and intensity of gastric juice corrosion.

The serious defect in the Leube, Lenharz, and all other types of medical management, in general use the world over, lies in the lack of accurate knowledge of what is actually being accomplished while the patient is under treatment. As a rule, if pain and other symptoms are well controlled, no attempt is made to determine accurately how much, if any, the duration or intensity of gastric juice corrosion is reduced. Pain of ulcer may be entirely absent when the aspirated stomach contents show varying, even high grades of free hydrochloric acidity. The peptic corrosion that occurs when a small quantity of free hydrochloric acid is present is approximately as great as when a high degree of free acidity exists. Unquestionably the lack of accurate control of the free acidity of gastric secretion is responsible for such failures as occur when the various types of medical management in general use are applied to the treatment of peptic ulcer.

When death, jejunal ulcer and serious complications, the result

of faulty technic, are excluded, the failures that occur when surgical treatment is applied are attributable to the same lack of efficient control of gastric juice corrosion. Gastro-enterostomy, when successfully performed, usually causes the stomach to empty itself of food and secretion in approximately normal time, but never appreciably earlier than the physiologic limit of normal time.

In 15 per cent. of a series of 80 cases tested by me after gastro-enterostomy, considerable food and secretion were recovered seven hours and as long as twelve hours after the ingestion of a motor meal consisting of ordinary food containing vegetables.

Ulcers of the stomach and duodenum are corroded as long as food and free hydrochloric acid secretion are present in the stomach. When gastro-enterostomy is performed for a duodenal or pyloric ulcer that is causing stagnation of food and secretion, the healing of the ulcer is benefited only proportionate to the number of minutes or hours that the duration of peptic corrosion is thereby reduced.

It must be remembered that after gastro-enterostomy, food and secretion continue to pass through the pylorus proportionate to the size of the opening that exists through the strictured area of the pylorus and duodenum. Only a small fraction of 1 per cent. of all cases of pyloric and duodenal ulcer for which gastro-enterostomy is now regularly performed are near the danger point of starvation because of the narrowness of the opening at the outlet. The average case has lost only moderately in weight. Such loss of weight as does occur is nearly always due to voluntary restrictions in diet because of pain, and not because the opening is actually narrowed to such a degree that sufficient nourishment is unable to pass through.

Any one sufficiently interested to study accurately cases after gastro-enterostomy by means of the Roentgen ray will easily demonstrate to himself that food and secretions are pushed through the pyloric orifice proportionate to the size of the opening at that outlet. When Roentgen-ray meal of the consistency of food is used, the musculature is seen to force the stomach contents against the pyloric outlet with such persistent vigor that none can doubt that the major portion of all food and secretion passes through the pyloric outlet within a short time after gastro-enterostomy is per-

formed. In every case after gastro-enterostomy, unless the pylorus is occluded by operative procedure, a sufficient quantity of gastric juice is poured through the pyloric outlet to keep the ulcer constantly bathed in the corrosive secretion until the stomach has emptied itself of food and secretion.

A duodenal ulcer after gastro-enterostomy is placed in no more favorable conditions for healing than attend the usual untreated stomach ulcer located distant from the pylorus, or for other reasons unassociated with stagnation of food and secretion. The duration of corrosion in both instances equals that of the normal digestion period, which is several hours each day. The symptomatology of a duodenal ulcer after gastro-enterostomy is similar to that of the ordinary untreated stomach ulcer unassociated with stagnation of food and secretion.

That a duodenal ulcer treated by gastro-enterostomy usually heals in the course of time, and meanwhile is likely to cause but few serious symptoms, is consistent with the probable fact that the majority of stomach ulcers, located, as they are, on the lesser curvature or posterior wall and distant from the pylorus, usually give rise to few serious symptoms and heal without treatment.

Probably only such stomach ulcers as are located at or very near the pylorus, or that penetrate to or beyond the peritoneal coat, or become unusually large, or cause hemorrhage, or develop malignancy, produce serious symptoms.

If the commonly accepted conception of peptic ulcer is correct, namely, that the digestive action of the gastric juice constitutes the greatest hindrance to healing that is amenable to medical and surgical control, then it must follow that the healing of peptic ulcer is promoted most by that type of management which reduces to the greatest degree the duration and intensity of gastric juice corrosion.

No operative procedure as yet devised enables the stomach to empty itself of food and secretion appreciably earlier than normal time. Hence no operative procedure except excision of the ulcer or pyloric occlusion with gastro-enterostomy for duodenal and pyloric ulcer results in protecting a peptic ulcer from the corrosive effects of the gastric juice during the several hours each day occu-

pied by normal stomach digestion. My experience has demonstrated beyond question that it is entirely possible and remarkably easy to exercise practically absolute control over peptic activity for many months, and, if necessary, for years.

The gratifying results to be obtained by applying the treatment or the principles involved in the treatment of cases ordinarily regarded as absolutely intractable to medical management, including such cases as gastro-enterostomy and other surgical procedure legitimately applied have failed to relieve, demonstrate that there can be no lack of incentive for the internist to develop a technic in the medical management of peptic ulcer that is as accurate and painstaking as that required of the surgeon in performing gastro-enterostomy or pyloroplastic operations.

In my service at the Presbyterian Hospital, surgical procedure in the treatment of peptic ulcer is limited to the following complications and conditions that attend ulcer:

1. Perforation.
2. Perigastric abscess.
3. Secondary carcinoma.

When, after careful study of the case, there is a reasonable reason for suspecting that a carcinoma is developing at the seat of an ulcer, if no contra-indication exists, the ulcer-bearing area should be widely resected, with due regard to lymphatic distribution.

4. Hour-glass or other rare deformity of the stomach that is causing serious symptoms.

In very exceptional cases the history of Roentgen-ray examination may give evidence of a large, deep, excavated ulcer, and justify an attempt to excise the ulcer, or perforate it with a cautery, and then lessen its size by suture.

5. Foci of infection about the roots of teeth, in the tonsils and elsewhere in the body are sought and removed.

Rosenow's contribution to the etiology of peptic ulcer is of the utmost importance relative to the recurrence of ulcer and the prophylactic treatment of the disease.

It is manifestly useless to talk about the end result of any form of treatment of peptic ulcer when the patient harbors an alveolar abscess. An abscess about the root of a tooth may be responsibile for recurrences of ulcer extending over a period of years.

6. Hemorrhage of serious nature from peptic ulcer is a direct result of corrosion of bloodvessels by the gastric juice. Such corrosion is impossible when the digestive action of the gastric juice is annulled by accurate medical management.

Since serious bleeding practically never occurs after the first week of medical management, as outlined, surgical treatment is considered only in connection with patients who are bleeding when first seen, or within the first week after treatment is begun.

The results of surgical intervention when instituted for the control of serious hemorrhage at the time it is occurring are admittedly not encouraging.

I have subjected relatively very few cases to surgical operation for the control of hemorrhage.

7. Pyloric obstruction of high grade due to actual cicatricial narrowing that fails, under the influence of accurate medical management, to yield sufficiently to allow a motor meal to pass in normal time.

Operative experience shows that of all cases of duodenal and pyloric ulcer presenting definite clinical evidence of obstruction at the outlet, less than 10 per cent. are found at operation to be associated with an actual tissue narrowing of serious grade.

I differentiate two clinical types of pyloric obstruction resulting from ulcer:

1. Pyloric obstruction due to conditions easily removable by two weeks of the accurate medical management advocated. More than 90 per cent. of all cases of pyloric obstruction due to ulcer are of this type.

2. Pyloric obstruction due to anatomic narrowing from infiltrated tissue, some of which may be cicatricial tissue in varying stages of development.

The probable cause of the first is pyloric spasm, inflammatory swelling, and at times, perhaps, a local peritonitis.

If at the end of two weeks of accurate medical management, during which the acidity is properly controlled both night and day, a full motor meal is given and 100 c.c. or more of food is found at the end of seven hours, an actual anatomic tissue narrowing exists, in practically all cases, unless nausea or some other condition is interfering temporarily with the motor power.

I formerly subjected such cases to gastro-enterostomy.[1] As previously stated, with reasons given, I am now convinced that unless the opening is so very narrow that death from starvation is threatened, the size of the opening will practically always increase —if both day and night corrosion is accurately controlled. Experience to date with the method has shown that as yet none has failed to open up sufficiently to allow the stomach to empty itself of a full meal in seven hours.

When the pyloric outlet is large enough to permit the stomach to empty itself of a full meal within the limit of normal time, it is useless to perform gastro-enterostomy for peptic ulcer at the pyloric outlet or elsewhere. When an ample pyloric outlet exists, the healing of peptic ulcer can be hastened only by such means as can bring about a reduction of the duration of gastric juice corrosion to a shorter period than that occupied by normal stomach digestion. No operative procedure accomplishes this except when a duodenal or pyloric ulcer is treated by gastro-enterostomy combined with pyloric occlussion.

The medical management advocated accurately protects the pyloric and duodenal ulcer from gastric juice corrosion, and thus renders gastro-enterostomy combined with pyloric occlusion unnecessary. Gastro-enterostomy combined with pyloric occlusion is not without mortality when performed by those most expert. The mortality of such and all other operative procedures when performed by the rapidly increasing number of those who conscientiously attempt to imitate the expert is known best by those who through persistent endeavor have finally acquired a skill that is attended by a low mortality.

The medical management of peptic ulcer the world over is today practically the same as that advocated by Leube, Riegel, and others of twenty-five years ago. Such medical management is efficient, to a certain degree. The general tendency for a peptic ulcer to heal if Nature is aided but slightly is responsible for the cures that can be brought about by it. The majority of all uncomplicated ulcers heal under its influence. No doubt many cases of duodenal ulcer can be cured by it.

[1] Musser and Kelly, iii.

If no more accurate means of medical management are at hand, surgical treatment has a very wide field of usefulness in the management of peptic ulcer. It may legitimately be applied only to such conditions and complications of peptic ulcer as are mechanically relievable or removable, and with reasonable safety to the patient.

The old and generally accepted belief that gastric juice corrosion is the most important influence that retards the healing of ulcer receives confirmation from the results that are obtained by all methods of treatment that have contributed to the healing of ulcer.

If the commonly accepted conception relative to gastric juice corrosion is correct, the number of cases of peptic ulcer now generally considered legitimately operable may be enormously reduced by the careful application of the method of medical treatment advocated.

The striking result to be obtained by applying the principle of accurately protecting the ulcer from gastric juice corrosion would seem to be the best evidence yet produced in substantiation of the old corrosion theory of peptic or digestive ulcer.

For the purpose of lessening the great confusion that has attended the problem relative to the treatment of peptic ulcer since the days of the first successful gastro-enterostomies, I recommend the application of earnest thought to the three fundamental questions, as stated in the beginning of this article. It is only by persistent effort directed toward a rational solution of these essential questions that the greatest progress in the treatment of peptic ulcer is to be attained:

1. What are the causes of peptic ulcer?
2. What retards or prevents the healing of peptic ulcer?
3. What can we as physicians and surgeons do to promote best the development of granulation tissue essential to the healing and final cicatrization of peptic ulcer?

DISCUSSION

Dr. L. F. Barker: Having heard from the surgeon whose name will always stand with that of Moynihan in the history of the therapy of duodenal ulcer, and from a medical clinic of such note as that represented by

Dr. Billings and Dr. Sippy, comment from others would almost seem superfluous. But differences of opinion still exist between physicians and surgeons as regards both diagnosis and therapy.

The diagnosis of duodenal ulcer is easy in typical cases and no one need mistake them. But medical men see so many cases of "hyperchlorhydria" which they do not believe to be due to ulcer that, although Moynihan seems to believe them all due to ulcer, medical men are, and will continue to be, skeptical until more convincing evidence is brought. In the diagnosis of doubtful cases, we, who work in internal medicine, find a real help in roentgenography, and, particularly, in serial roentgenography. From chronic cholecystitis, pericholecystitis, chronic pancreatitis, and chronic appendicitis the differentiation of duodenal ulcer may be very difficult at times, and the findings at operation, even when exhaustive clinical studies have preceded it, are often disappointing, or surprising.

As to the best methods of therapy, many questions are still open. When there is extensive hemorrhage, duodenal obstruction, or threatened perforation, surgery is, undoubtedly, our only proper recourse. But in the milder cases we are still often in doubt; gastrologists like Julius Friedenwald and B. W. Sippy tell us that they see many recoveries under medical management. Moreover, the results of surgical procedure are far from being uniformly satisfactory, as is notorious. There may be some significance in the fact that recent graduates in medicine, when they suffer from duodenal ulcer, themselves, tend to be operated upon, while the older men, at least in my experience, tend to prefer first a thorough trial of medical treatment.

Medical men and surgeons must continue to work together on this important problem, until through the interchange of opinion and experience, we are, at length, placed in the position in which we may speak positively, in every case, regarding the most desirable therapeutic measures to employ.

Dr. William H. Welch: Among the notable achievements of recent years have been the contributions of the surgeon to pathology and internal medicine, and among these none are more valuable and remarkable than those coming from the clinic of the Doctors Mayo, of which an example has been presented to us today in the paper by Dr. W. J. Mayo.

Dr. Mayo has justly commented upon the contrast between the older methods of investigation of gastric and duodenal ulcers and those now available, especially through the observations of the surgeon. More than most diseases ulcer and cancer of the stomach have been studied in the past by the statistical method of analysis, a method in which Brinton led the way, adopting the procedure of Louis. Notwithstanding the apparent precision of this statistical method, the conclusions derived from it were in several important respects inaccurate, as has been so convincingly demonstrated by the results obtained at the Mayo Clinic.

Among the most striking of these newer results have been the evidence regarding the hitherto unsuspected frequency of duodenal ulcer and the demonstration that many ulcers formerly regarded as originating in the pyloric regions in fact have their origin in the upper part of the duodenum. It is true that the surgical observations upon which these newer views are based cannot safely be regarded as revealing the frequency of duodenal ulcer in all classes of persons. They indicate the incidence of the affection in patients seeking surgical relief under the conditions of the clinics reporting these figures. Further observations from all sorts of sources, especially from postmortem examinations of open and of healed ulcers, are needed to determine the actual frequency of occurrence of duodenal and gastric ulcers, but such observations must take full cognizance of the experience derived from surgical practice.

Dr. Sippy's interesting studies will, I conceive, need further experimental support before we can apply them confidently to the very puzzling question of the pathogenesis of gastric ulcer. The problem is quite as much to explain why the defect caused by the ulcer does not heal as how it starts. Defects in the gastric mucosa and submucosa produced experimentally heal as readily under ordinary circumstances as similar defects elsewhere.

Dr. Frank Billings: Rosenow's work on the relation between infectious foci and ulcer, both of stomach and duodenum, will certainly receive more consideration in the etiology of these conditions than heretofore, and will be found to have a bearing on the non-healing of ulcers. Moreover, it will be accepted that failure to treat infectious foci will invite recurrences of ulcer.

Spasm and hypertrophy of muscle, together with infiltration of tissues, as a contributing cause, may produce obstruction; this must be admitted, because from ulcers so situated that these factors can not cause obstruction no such severe symptoms arise and thus no diagnosis is made except of hyperacidity. In watching Dr. Sippy's work, I have too often seen obstructive symptoms disappear to doubt that they can both originate in the way indicated and that they can be dissipated with the healing of the ulcer under medical management.

Dr. A. McPhedran: It seems important to remember that after gastro-enterostomy the gastric peristalsis is still toward the pylorus and the contents pass into the duodenum as they did before the operation. As the pylorus closes the current of food is returned along the greater curvature and thus to the gastro-enterostomy opening through which it passes more or less freely. This can be seen by the aid of the fluoroscope. It therefore must follow that the benefit of the short-circuiting is due to the earlier and complete emptying of the stomach, thereby relieving it of its irritating contents. If by medical means the gastric contents can be rendered bland

and non-irritating so that they may be promptly and completely discharged through the pylorus as described by Dr. Sippy, the *raison d'être* of gastro-enterostomy will have ceased. The difficulty, however, is to render the contents nearly or quite neutral and maintain them so until the stomach has been emptied. This can be done probably only in the early stages, that is, before the ulcer has become indurated.

Dr. E. Libman: Our experience at the Mount Sinai Hospital has been that the duodenal ulcers are more frequent than the gastric ulcers, in this respect coinciding with the experience of Dr. Mayo. We have also come to believe, as he does, that the presence or absence of occult blood in the stool is of no great value in diagnosis. One of the most important points in the diagnosis of duodenal ulcer is the history of complete remissions. In cases of chronic appendicitis and cases of cholelithiasis, resembling cases of ulcer, remissions may occur, but in the free period there is not the complete freedom from symptoms that there is apt to be in the ulcer cases. Not enough attention has been paid to the fact that in a certain number of cases of ulcer of the duodenum, the first pain is to be found in the left iliac fossa,—at times shooting into the lumbar region. Later in such cases the position of the pain is apt to change to the typical location.

Dr. Julius Friedenwald: In reference to Dr. Mayo's and Dr. Sippy's papers, I should like to state that according to our statistics we have observed 52 per cent. of duodenal ulcers to 40 per cent. of gastric ulcers.

Dr. Baetjer and I have shown, two years ago at the meeting of this Association, a definite method by means of the *x*-ray of differentiating between gastric and duodenal ulcer. In gastric ulcer we have retention, hour-glass formation, and spasticity of the pylorus frequently, in addition to filling defect, while in duodenal ulcer there is a hypermotility, and a vacant area in the duodenum. The two conditions can therefore be easily distinguished in uncomplicated cases. Whenever possible, Dr. Finney prefers pyloroplasty to gastro-enterostomy. From a comparison of 100 cases of both operations, which Dr. Finney and I have just reported, the immediate as well as the end-results have been greatly in favor of pyloroplasty, there being a percentage of 88.6 per cent. of satisfactory recoveries with pyloroplasty and but 77.2 per cent. with gastro-enterostomy.

Dr. C. F. Hoover: There may be a difference between the ease of locating ulcers on the distal side of the pylorus and the proximal side. Dr. Mayo's results were arrived at by the direct evidence of inspection of the serosa, inferentially concluding that the appearance of the serosa is a dependable index of the condition on the inside of the gut. I recently saw a case of suspected duodenal ulcer in which no ulcer was found at operation, but in which afterward an enormous ulcer was found

on the proximal side of the pylorus and not indicated by any appearance on the serous surface. Thus gastric ulcers may be missed even after surgical inspection of the organ.

Dr. S. Solis Cohen: It is not wise to lay too much stress upon hyperchlorhydria as a positive sign of ulcer either of the stomach or of the duodenum. Neither can we accept hypochlorhydria as conclusive evidence against ulcer. The work of Rehfuss and Hawk at the Jefferson Hospital shows that our methods of examination must undergo revision; especially as regards the time of maximal secretion. We must take the whole curve, not a part of it. A process cannot be judged from an instant.

The demonstration of hypermotility, however, is a great aid in the diagnosis of duodenal ulcer; not pathognomonic, of course, but weighty. I would strongly urge the personal observation by the physician of the gastric and intestinal movements on the fluoroscopic screen. Not only is this far more satisfactory than mere inspection of plates, but unless the physician constantly works with the roentgenologist, neither can interpret correctly the findings, nor can the true value of special phenomena be settled definitely.

Dr. Louis B. Wilson: I wish to call attention to two types of lesions of the gastroduodenal tract, which evidently present unusual diagnostic difficulties. These are ulcers low in the duodenum, two or three inches below the pylorus, and cancers of the cardia. Lesions involving these extreme limits of the ulcer and cancer-bearing area may readily escape not only clinical observation but also the observation of the surgeon at the operating table.

Dr. H. G. Wells: Dr. Mayo spoke of the occurrence of ulcer at the site of operation. Some experiments that are being carried out in Prof. Carlson's laboratory seem to offer an explanation of this. In dogs with a Pawlow stomach injections of strains or streptococci from ulcer cases, obtained from Dr. Rosenow, have produced typical gastric ulcers and permitted the study of the secretion of the stomach before, during and after the formation of the ulcer. In these dogs the ulcers tend to occur at the points of operative injury, obviously because there a place of lowered resistance exists. Is it not also probable that when a surgeon performs gastro-enterostomy or other operation on the stomach of a patient with gastric ulcer, without first removing the source of the bacteria that have produced the ulcer, he actually invites the production of more ulcers in the places of lessened resistance created by his operative procedure?

Dr. M. G. Fussell: As has been said physicians are constantly treating cases of so-called hyperchlorhydria. When such cases are thoroughly

studied under careful dietetic management and with the aid of roentgenoscopy, they separate themselves into their proper classes: those that do not improve under medical treatment are regarded as surgical cases and by the competent physician are referred to the surgeon.

Dr. Wm. J. Mayo: I must apologize for the apparent flippancy of my remarks upon the diagnosis of duodenal ulcer; what I had in mind was the fact indicated in Dr. Brown's paper that there are many factors involved in the duodenal problem which are not involved in the gastric problem; the approach to the study of the subject must therefore be different.

One settled conviction I wish to emphasize: if the surgeon cannot demonstrate the presence of an ulcer, such a stomach or duodenum should not be operated upon regardless of the symptoms.

My practice is to excise gastric ulcers whenever possible; and to excise duodenal ulcers if the excision does not add surgical risk.

With regard to Dr. Sippy's paper and to Dr. Billing's remarks, I have never known scar tissue in the duodenal or gastric mucosa to stretch any more than such tissue does elsewhere, but it is perfectly true that if obstructive symptoms are due to edema and muscle spasm alone, relief of the obstruction will follow any measure which will abate the edema and spasm.

As to Rosenow's work, I have found, as have others, that in cases of acute perforation, when the opening is clean cut and recent, the cases get well with simple repair of the perforation and some get well spontaneously; if further trouble appears it will be the result of mechanical condition brought about by the contraction and for this reason gastro-enterostomy should be done if practicable.

In view of the discussion, I should perhaps change my title to "The Surgical Treatment of Non-healing Duodenal Ulcers;" and fully agree that those cases that have a chance to get well under medical treatment should be given an opportunity to do so.

BLOOD TRANSFUSION: INDICATIONS; RESULTS; GENERAL MANAGEMENT[1]

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AND

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Blood transfusion, until recently, was expected to be a cure-all, and was tried in almost every kind of desperate condition. As the result of a large amount of work done since Crile's introduction of a successful technic for direct blood transfusion,[2] the real indications for transfusion have become better understood and more sharply defined. Crile's statement of the indications have, for the most part, remained valid, but subsequent experience has altered our views in regard to many of them. In particular, the indications for transfusion have been extended by two facts: transfusion has become safe, and transfusion has become a much less serious procedure for both patient and donor. Clinical experience has shown that the tests for agglutination and hemolysis between blood of donor and of patient are reliable,[3] and except in the relatively uncommon emergency case in which there is not time to do these tests, we now approach a transfusion with absolutely no fear of this lurking danger. The danger of excessive transfusion (of which two instances occurred among the earlier of our cases) can be easily avoided—for direct transfusion by a simple method of calculation introduced by us,[4] and for indirect transfusion by accurate measurement of an amount of blood predetermined by such a calculation. The simplifications of technic, and especially the introduction of a good method of

syringe transfusion by Lindeman,[5] have made transfusion a procedure which involves little trauma or pain, and which can be repeated on the same patient as often as desired. As a result of all this the tendency is more and more to use transfusion not as a means of last resort but as an ordinary therapeutic measure.

In the present paper we have made a clinical study of 212 blood transfusions in 189 cases which we have had the opportunity of observing either in the hospital or in private practice. These transfusions were done by a number of different surgeons, and for a great variety of different conditions.[6] In many of the cases the indications had been established by previous work: on the other hand some of the transfusions were practically experimental. Of these, some were successful and others, in the light of the experience thus gained were cases in which even under the best possible conditions little or nothing can be expected from transfusion.

We shall refer only incidentally to the now rapidly growing literature, as we believe that more will be gained by presenting our own conclusions fully and leaving it to the reader to compare them with those of others.

We shall first briefly summarize the general results of all the transfusions (Part I) and shall then discuss in detail the results in each of the conditions for which transfusion was done (Part II); and finally (Part III) we shall discuss certain details concerning the general management of transfusions.

Part I

General Summary of Results

One occasionally hears the opinion put forward that transfusion after all has not turned out to be a useful procedure, that there are few cases in which it really does good, and that it will probably be dropped again just as it was thirty years ago after the wave of enthusiasm for it following the Franco-Prussian War. For this reason we present the following general summary of the successes and failures in the 189 cases which we have seen. The proportion

of successful results in the future will undoubtedly be far greater than in the past, not only because of recent technical improvements but because the indications will be more definitely known and the discrediting transfusions in hopeless cases, in which transfusions can not possibly be of avail, will not occur. The cases are subdivided according to the following scheme:

I. Successful cases.
   1. Cases in which the prognosis was extremely bad, and transfusion saved life.
      (*a*) Cases which subsequently completely recovered.
      (*b*) Cases in which the original underlying disease continued.
   2. Cases which recovered but in which the prognosis before transfusion was not desperate.

II. Unsuccessful cases.
   1. Cases in which there was temporary improvement following transfusion, with death later from continuation of the original disease.
   2. Cases which died of some disease necessarily fatal and in which transfusion could not have been expected to do much good.
   3. Cases in which transfusion did little or no good, although from the nature of the disease a good result might have been possible.

I. Successful Cases. 1. *Cases in Which Transfusion Saved Life.* There are 42 cases of this kind—that is to say, cases which almost undoubtedly would have died in a short time if transfusion had not been done. Of these, 29 subsequently recovered entirely and were discharged well or have continued under observation up to the present time; 13 were saved from immediate death but have continued to suffer from some chronic condition which could not have been cured by transfusion (pernicious anemia, leukemia, etc.).

(*a*) *Cases Which Ultimately Recovered.* Almost all the 29 cases which were rescued from immediate death were cases of hemorrhage. There were 9 cases of gastric or duodenal ulcer with extreme hemorrhage; 3 cases of hereditary hemophilia; 3 cases of ectopic pregnancy; 7 cases of hemorrhagic diathesis; 1 case of sloughing

uterine fibroid with hemorrhage; 1 case of cholemic hemorrhage; 1 case of hemorrhage after a kidney operation; 1 case of illuminating gas and morphine poisoning; 1 case of typhoid hemorrhage.

(*b*) *Cases in Which Life was Saved by Transfusion, but in Which the Underlying Disease Continued, or Which Ultimately Left the Hospital in Greatly Improved Condition or Are Still under Observation.* These 13 cases include 6 patients with pernicious anemia who lived for long periods after apparently life-saving transfusions; 2 cases of cancer in which persistent hemorrhages stopped; 1 case of hemorrhagic diathesis with grave anemia, who left the hospital in improved condition against advice; 1 patient with a tumor of the spleen and grave anemia of unknown origin and 1 case of chronic leukemia.

The cases, then, in which transfusion was apparently life-saving fall under four main headings:

Acute anemia from hemorrhage.

Hemorrhagic diathesis, whether hereditary or acquired.

Grave chronic anemias.

Poisoning.

2. *Cases Cured or Greatly Benefited, Not in Desperate Condition at Time of Transfusion.* There were 43 cases in which transfusion was not an emergency measure but was performed on patients whose general condition had been seriously impaired by chronic disease. Most of these patients ultimately made complete recoveries, others continued to suffer from the chronic illness. In all the cases there was great improvement following the transfusion.

There were among these, 3 cases of gastric or duodenal ulcer which had repeated hemorrhages but were not in desperate condition at the time of transfusion. Undoubtedly recovery in these cases was greatly hastened by transfusion. The same may be said of 2 cases of dysentery with marked anemia. In this group also were 9 cases of pernicious anemia with marked remissions; 3 of the cases were instances of severe infection from osteomyelitis, in which the increased strength given by transfusion undoubtedly brought about the ultimate recovery; 9 were cases of malignant disease which were greatly benefited by the transfusion, 3 of them undergoing subsequent radical operations.

Of the 189 transfusion cases, then, 85 (or 45 per cent.) were successful in that the condition of the patient was greatly improved, and 42 of these (or 22 per cent. of the whole number) were life-saving.

II. Unsuccessful Cases. There were altogether 104 cases in which transfusion did no good or in which the continuation of the original disease caused death. (This is exclusive of a few early cases, not enumerated in the present series, in which the operation of transfusion itself was not successful, *i. e.*, no blood, or very little passed from donor to patient.)

1. There is a first group of 28 cases which improved for a short time but died subsequently from continuation of the original disease. These included a considerable variety of diseases, chief among which were malignant tumors, pernicious anemia, subacute streptococcus endocarditis, dysentery, typhoid fever, and pyogenic infections. These were all cases which lived from several days to one and a half years after transfusion.

2. The second group of the cases which died consisted of 23 cases of some disease of itself so grave that transfusion could not have been expected to do much good, and was only resorted to as a desperate hope. These included cases of acute lymphatic leukemia (3 cases), typhoid perforation (1 case), brain tumor (1 case), diabetic coma (3 cases), uremia (1 case), hemorrhagic diphtheria (1 case).

3. The third group of fatal cases consisted of 23 patients in whom transfusion might have been expected to be beneficial, but actually did little or no good. Of these the most disappointing were 4 cases of postoperative shock and 6 cases of pathological hemorrhage (including 4 of cholemia and 2 of purpura hemorrhagica). In these instances, contrary to expectation, the hemorrhages were not influenced by transfusion. There were also 3 cases of hemorrhage in typhoid fever.

Finally, there were 2 cases (1 of pernicious anemia and 1 of subacute streptococcus endocarditis) in which the unfavorable outcome was hastened by transfusion of excessive amounts of blood and 3 cases in which the fatal result was probably due to transfusion of incompatible (agglutinative and hemolytic) blood.

Part II

SPECIAL INDICATIONS

These are subdivided according to the following scheme:

I. Transfusions for simple hemorrhage.
   1. Gastric and duodenal ulcer.
   2. Dysentery.
   3. Typhoid hemorrhage.
   4. Ectopic pregnancy.

II. Transfusions in connection with surgical operations.
   1. Preliminary to operation.
   2. For postoperative hemorrhage.
   3. For shock.

III. Transfusions for the cure of hemorrhagic conditions.
   1. Purpura hemorrhagica.
   2. Hemophilia.
   3. Hemorrhages secondary to
      (*a*) Blood diseases.
      (*b*) Severe infections.
      (*c*) Jaundice (cholemia).

IV. Transfusions for blood diseases.
   1. Pernicious anemia.
   2. Leukemia.

V. Transfusion for infections.
   1. Infections with pyogenic organisms.
   2. Subacute streptococcus endocarditis.

VI. Transfusions for intoxications.
   1. Acute poisoning.
   2. Diabetic coma.

VII. Transfusions for debilitated conditions.
   1. Cancer.
   2. Malnutrition.
   3. Simple anemia.

I. Transfusions for Simple Hemorrhage. 1. *Gastric and Duodenal Ulcer.* There were altogether 14 cases of gastric or duodenal ulcer transfused. Almost all of these were in desperate con-

dition at the time the transfusion was done; 12 of the 14 recovered. The 2 deaths occurred not from a continuance of the hemorrhage but from peritonitis and other complications following the laparotomy. Of the 12 cases which recovered, 4 were cases of duodenal and 8 of gastric ulcer. In all the cases there was a severe anemia, and actual hemorrhage was still going on at the time of the transfusion.

The hemorrhage in these cases was slight at the time, probably due to exsanguination, and the transfusion seemed to exert a beneficial effect on the hemorrhage itself.

Of the 2 cases which died, 1 was a case of duodenal ulcer, 1 a case of multiple gastric ulcers complicated by a cholecystitis; 1 of these cases continued to bleed after the transfusion. Death in this case was not due to the bleeding, however, which was relatively slight, but to a general peritonitis following pylorectomy.

The results in the gastric and duodenal ulcers show that transfusion exerts an exceedingly favorable effect on hemorrhage. It should be said that the two fatalities in ulcer cases were among the three operated cases, but that in these three cases the operation had to be performed for other indications than hemorrhage.

There were 4 additional cases of severe gastro-intestinal hemorrhage not included in the list of gastric ulcers. Only 1 of these recovered. One was a patient who had been suffering from a chronic anemia with a large spleen for a year or more, and who suddenly had a profuse gastric hemorrhage. A large transfusion was done, but the hemorrhage continued and the patient died within twelve hours. It seems likely that the hemorrhage may have been due to thrombosis of the splenic vein. Another was a case of profuse gastric hemorrhage secondary to cirrhosis of the liver; this case recovered. The third was a fatal case of postoperative gastric hemorrhage following extirpation of the rectum for carcinoma; and the fourth, a case of hemorrhage from a carcinoma of the stomach in which the patient died after a subsequent operation.

It is a striking fact that in almost all the cases of gastric or duodenal ulcer the hemorrhages stopped after transfusion. At first there was considerable hesitation about transfusing these cases during active hemorrhage on account of the danger of raising the blood-pressure and thus increasing the hemorrhage. This danger

undoubtedly does exist, and because of it we would warn against transfusion in acute first hemorrhages (except for the purpose of saving the patient from immediate exsanguination).[7] *The cases in which transfusion seems actually to check hemorrhage are those of repeated or prolonged bleeding.* In these cases (as anyone who has tested the coagulation time of many patients has observed) the coagulation time of the blood is normal or even shortened, but the clots are of a flabby nature, different from the firm tough clots of chronic anemias. It seems likely that these soft clots form imperfect thrombi and thus the mere prolongation of a hemorrhage causes a vicious circle and tends toward its further prolongation. Transfusion checks the hemorrhage by supplying blood which can form normal thrombi.

The same explanation of the hemorrhage-checking effect of transfusion applies, of course, not only to gastro-intestinal, but to other forms of prolonged hemorrhage, and partly to the hemorrhagic diatheses.

2. *Dysentery.* There were transfusions in 6 cases of severe dysentery. These patients were all profoundly anemic, due not only to hemorrhage, but to nutritional disturbance. In all the cases the immediate results of the transfusions were very good, but in 4 of the 6, the intestinal disturbance continued and the patients ultimately died. In one of the patients the dysentery finally yielded to treatment and recovery ensued. In 1 the general condition was bettered, but the patient has continued to suffer from intestinal symptoms.

In severe dysentery, then, transfusion is worth trying as a temporizing measure.

3. *Typhoid Fever.* As the chief indication for transfusion in typhoid fever is usually hemorrhage, all the cases of typhoid fever will be summarized here. There were nine transfusions in 7 cases of typhoid fever. Of the 7 patients, all in the most desperate possible condition, 2 ultimately recovered. One of the fatal cases should perhaps be excluded, as it was a case of intestinal perforation in which transfusion was done in the hope of bringing the patient, already in profound shock, into a condition in which an operation could be done. The transfusion was without effect. The

6 other patients suffered from severe and protracted hemorrhage. In the 2 who recovered the hemorrhage practically ceased after the transfusion. Of the 4 who died, 3 had hemorrhages so large that transfusion could accomplish nothing. In the fourth the hemorrhages stopped for a time after transfusion only to begin again after a few days. Two weeks later a second transfusion again relieved the symptoms due to hemorrhage, and the bleeding stopped. The fever continued and the patient died three weeks later of exhaustion. If, as seems fair, we include the two transfusions in this case among those in which the symptoms of hemorrhage were relieved by transfusion, we can say that there were four such transfusions among the seven done for typhoid hemorrhage.

One of the 2 cases that recovered has been reported by Dr. Manges,[8] with whom we had the privilege of observing the patient. In this case two transfusions were done. After the first the hemorrhage ceased. There continued, however, a remarkably protracted and severe typhoid infection, and there developed a general streptococcus infection. A second transfusion was done a month after the first, and the patient recovered with surprising promptness.

As the two patients who recovered would in all probability have died without transfusion, it is undoubtedly a useful method in the treatment of severe typhoid fever. In the presence of exceedingly large hemorrhages it can have, of course, only a temporary stimulating value. In cases of protracted or repeated hemorrhage it not only replaces the lost blood, but may help check hemorrhage. (See above under Gastric Ulcer.) *In all typhoid cases the first appearance of blood in the stools should be an indication to make preparations so that a transfusion can be done, if needed, at very short notice.* If the transfusion is not needed, little is lost; if it is needed, invaluable time is gained. Finally, in the typhoid state and in very protracted cases of typhoid, transfusion may have life-saving value and should be tried oftener than it has been.

4. *Ectopic Pregnancy.* There is perhaps no single condition to which transfusion would seem to be more ideally suited than ruptured ectopic pregnancy. There were three such cases in our series, and in all of them the transfusion was life-saving. The

circumstances of the transfusion in the three cases differed slightly. The one was an emergency case, an almost exsanguinated patient, and a transfusion was done immediately after the operation. Another had been operated upon, but two days after the operation she was doing badly and a large transfusion was done. The third was a case which bled slowly and in which the diagnosis was at first not certain. A transfusion raised the hemoglobin from 25 to 50 per cent., and a successful laparotomy was performed two days later.

II. Transfusions in Connection with Surgical Operations. 1. *Preliminary to Operation.* Among the most satisfactory transfusions in the whole series were some of those done preliminary to an operation upon patients whose desperate condition would otherwise have contra-indicated any operation. There were 33 such preoperative transfusions and in 13 of them the result was decisive and the patients recovered. The actual effects of such transfusions are even better than these figures show, because a majority among those that died did so as a result of postoperative complications (such as peritonitis or pneumonia) or of a continuation of the original disease (such as metastatic carcinoma). Three died of operative shock; and our experiences have not led us to think that transfusion has any specific effect in preventing shock further than its effect in restoring to the patient more or less of his original power of resistance.

2. *For Postoperative Hemorrhage.* Little need be said about postoperative hemorrhage that has not been said about hemorrhage in general. Transfusion is the ideal remedy, but, of course, if the hemorrhage is not at the same time checked the ultimate outcome will not be affected. There were 5 transfusions for hemorrhage after operation (not including the transfusions for postoperative hemorrhage due to cholemia, which will be discussed separately). In 3 of the cases there were brilliant recoveries, in 2 death. In the 2 fatal cases (nephrotomy and operation for malunion of fractured femur) shock probably played almost as large a role as hemorrhage. (In the former of them transfusion of incompatible blood may have been a contributing factor.[9])

3. *For Shock.* There were seven transfusions for postoperative shock. All the patients died within an hour to five days, and it

seems probable that transfusion is not to be relied upon clinically as a remedy for pure shock. In four of the cases (nephrectomy, bone-plating, prostatectomy, amputation of leg) hemorrhage played an important but secondary role. The results are the more disappointing as shock is one of the conditions in which it was at first thought, from the experimental work of Crile and his collaborators, that transfusion would be life-saving. This much, however, is to be said about our results: the transfusions were all done late, after the shock had lasted for some hours to several days. It is possible that if the condition of shock could have been foreseen and transfusion done immediately after the operation instead of after many hours of delay the results (especially in those cases combined with hemorrhage) might have been better.

III. Transfusions for the Cure of Hemorrhagic Conditions. The group of hemorrhagic diseases is a heterogeneous one comprising a number of conditions of very diverse pathogenesis. For practical purposes the 35 cases in our series can be grouped under (1) idiopathic purpura hemorrhagica, (2) hemophilia, and (3) secondary hemorrhagic disease complicating such conditions as severe infections, pernicious anemia, leukemia, and prolonged jaundice. Of hemorrhagic disease of the newborn, which has proved so brilliant a field for transfusion therapy, there was only one case in our series, and as the disease in this case was probably secondary to a staphylococcus infection, it will be included under the heading of secondary hemorrhagic disease.

1. *Purpura Hemorrhagica.* Idiopathic purpura hemorrhagica is characterized by the occurrence of spontaneous hemorrhages in various locations. The number of blood platelets is usually decreased greatly, but the coagulation of the blood is generally unimpaired. These two laboratory criteria were sought for and found in most of the cases of our series. The milder purpuras, as a rule, recover spontaneously. The more severe ones are frequently fatal, and it is only in this class of severe purpuras that transfusion is often used.

There were twelve transfusions in 9 such cases of severe purpura. Of the 9 cases, 2 died, uninfluenced except as to temporary replenishment of blood, 6 recovered completely, and 1 left the hospital

improved. More striking than the statistics (especially in a disease of which the milder cases usually recover) was the prompt cessation of hemorrhages in most of the cases. This phenomenon leaves little doubt that beside the effect of transfusion in replacing lost blood, it has a definite curative value in these cases. On what the curative value depends is at present not at all clear. It is evidently not due to restored coagulability of blood (as it is in hemophilia), for in purpura the blood clots normally. That it has some connection with the fresh supply of blood platelets seems likely. Platelets have been shown to possess an important function in thrombus formation quite apart from their role in mere blood coagulation. But the normal life duration of platelets is known to be very short, and it does not seem probable that the relatively limited supply of platelets, even in a large transfusion, can account for all the benefit produced.

Of the 9 cases, the 2 which were fatal form a peculiar group, because they were both cases of postpartum purpura hemorrhagica. In both cases the hemorrhages were entirely uninfluenced by rather large transfusions. It is possible that the pathogenesis of these cases is different from that of the others.

Of the 7 cases which recovered all were in desperate condition at the time of transfusion, in 6 of them the hemoglobin being reduced to between 10 and 25 per cent., and in the seventh, to 42 per cent. In 4 of these cases the cessation of hemorrhages was prompt and complete after transfusion. (In 1, however, a case with ecchymoses, hemorrhages from the gums and profuse uterine hemorrhage, the uterine hemorrhage recurred after four months. A hysterectomy was done and the patient recovered, and according to the notes supplied us by Dr. Maybaum the patient has remained well for seven months.) In the other 3 cases the cessation of hemorrhage after transfusion was not complete; slight subsequent hemorrhages did occur, but the turn for the better was unmistakable; 2 of them ultimately recovered completely; the third, in spite of three transfusions, was still suffering from purpura when she left the hospital after three months.

In all of these cases, before transfusion was resorted to, attempts were made to check hemorrhage by serum treatment—subcutaneous,

intravenous, or local use of human, horse, or rabbit serum—and entirely without effect. We will return to the subject of serum treatment under the heading of hemophilia.

2. *Hemophilia.* This disease is one in which transfusion may fairly be spoken of as specific therapy for the control of hemorrhages. The exact pathogenesis of the hemorrhages is not entirely understood, but what we do know throws considerable light on the mode of action of the transfused blood. When blood is obtained from the vein of a hemophiliac during an interval between hemorrhages, the coagulation time is enormously prolonged but the clot which finally forms is normal in texture and amount. Analysis shows that the delayed coagulation is due to deficiency in some element that goes to form thrombin (fibrin ferment). Experimenters are not all agreed as to which element is lacking, but the preponderance of evidence favors the view that the power of producing the activating substance (known under a variety of names—thrombokinase, thromboplastin, cytozyme) is diminished in the circulating blood. On the other hand (and this is a very striking fact) there is evidence that this activating substance is not lacking in the tissue cells. And this corresponds to the well-known clinical fact (confirmed by us in a number of cases) that in hemophilia, even when blood obtained directly by venipuncture shows greatly prolonged coagulation time, blood obtained from small cuts or pricks, clots in approximately normal time. It is clear that transfusion stops hemorrhage in hemophilia by supplying the patient's blood with the lacking element; and it is also clear (*a priori* as well as from our clinical experience) that such cures are not permanent, that sooner or later the fresh supply of thrombin-forming substance must become exhausted and the tendency to hemorrhage exist anew.

There were five hemophilia cases in our series. All were males; four were children. Three gave typical family histories. The fifth case was a boy of sixteen and no family history of bleeding could be obtained, but the hemophilia had existed from birth.

The first case was not anemic but had a history of repeated hemorrhages from various sources, and was admitted to the hospital with hemorrhages into several joints. After the transfusion there were no further hemorrhages, and the patient left the hos-

pital in good condition. He reëntered the hospital three months later with renewed hemorrhages into the joints and from a small wound. The second case was a brilliant cure, the child being almost completely exsanguinated before the transfusion. No further hemorrhages occurred after the transfusion. In the third case, in spite of a successful transfusion, bleeding from a small wound in the chin stopped for only twenty-four hours after transfusion. The patient was taken home against advice and lost track of. The fourth case was a child with protracted hemorrhage from a cut in the mouth. Bleeding stopped at once after an intravenous injection of 25 c.c. of whole blood from the father. The fifth case was a boy aged sixteen years, who had since birth had repeated hemorrhages from various parts of the body, and who twice underwent probably life-saving transfusions when almost exsanguinated. In each instance hemorrhage stopped at once after transfusion.

Including the two transfusions in the fifth case, we can then report six transfusions in hemophilia cases. In all but 1 of the cases the transfusion was only done after protracted hemorrhage had failed to yield to all other kinds of treatment, including serum treatment. In five out of the six transfusions the hemorrhage was checked promptly and the patients regained good health. In the 2 cases that could be followed for some time the tendency to hemorrhage reappeared after weeks or months.

Hemophilia is a disease with a high mortality. The majority of persons afflicted with it never reach adult life. (This is what has given rise to the erroneous statement that the disease is only transmitted by females.) Transfusion, it seems to us, offers a new hope for these doomed individuals, and we would suggest the following plan of procedure:

Every individual known to have hemophilia ought to have at his command several persons whose blood by previous tests[10] *is known to be compatible with his, and who are willing, when called upon, to give blood for transfusion.* These donors, if relatives of the patient, should have the possible existence of latent hemophilia excluded by blood tests as well as by consideration of the hereditary laws of the disease. Whenever serious hemorrhages occur, prompt transfusion should be done, preferably by the

syringe method, as this does not injure the vein, and hence allows for any number of future transfusions. It seems to us possible that by this system the majority of hemophiliacs might be enabled to lead a life of normal duration.

It seems to us, further, that in these cases the prophylactic effect of small transfusions (25 to 50 c.c.) repeated at long intervals (one to three months) would be well worth trying. Such injections of one or two syringefuls of unaltered blood could easily be performed as an office procedure by any one skilled in the syringe method.

Comparison of Transfusion with Serum Treatment. Almost all the hemorrhagic cases (including those to be described below) and a number of the cases of hemorrhage from other causes (such as typhoid ulceration and gastric ulcer) received subcutaneous or intravenous injections of fresh serum before transfusion was resorted to. Without going into details we believe we can say that the serum treatment was given a fair trial; the serum was used in large amounts and repeatedly. We have also had a considerable experience with serum treatment in cases which did not come to transfusion. In spite of the occasional cessation of hemorrhages after such serum injections we have not been able to convince ourselves that serum injections have any effect on hemorrhage. In 2 hemophilia cases (not transfused) the coagulation time was no shorter after than before serum injections (subcutaneous in one case, intravenous in the other).[11] On the other hand, we have often seen serum or defibrinated normal blood show an unmistakable effect in stopping hemorrhage when applied directly to small bleeding points.

The rationale of serum treatment and of transfusion for hemorrhagic conditions is indeed different. The active ingredient of serum is thrombin (fibrin ferment). Thrombin never exists in circulating blood but is formed only when blood is shed. When injected into the circulation it is at once neutralized by the antithrombin which exists in blood plasma. If it were not so neutralized it would cause intravascular clotting. Serum, therefore, cannot be expected to exert any thrombin action at a bleeding point distant from the point of injection. Whatever distant effect it has is probably

in the easily assimilable nutrition which it offers, or possibly the serum ingredients can be made over by the body into the predecessors of thrombin. Transfusion of whole blood, on the other hand, supplies the body at once with all the substances in plasma, cells and platelets necessary to elaborate thrombin at a distant bleeding point.

Nevertheless, on account of the favorable reports of others, and particularly on account of the successes reported in hemorrhagic disease of the newborn (a condition with which we have had little experience), we believe that serum treatment deserves a further clinical trial.

2. *Secondary (Symptomatic) Hemorrhagic Disease.* Hemorrhagic disease is frequently secondary to some other condition, such as severe infectious diseases, blood diseases (leukemia, pernicious anemia), and intoxications (nephritis, jaundice, etc.). It seems probable too that further study will show that many of the cases now classed as idiopathic are really secondary. There were 18 undoubtedly symptomatic cases in our series, 3 secondary to infections, 5 to leukemia, 1 to pernicious anemia, 8 to cholemia (prolonged jaundice), 1 to nephritis.

The pathogenesis of the hemorrhages in these secondary cases is variable, as Whipple and others have shown. In some, deficiency in fibrinogen, in others a lack of some of the ferment-forming substances, and in still others an excess of antithrombin have been demonstrated. Whatever the pathogenesis, however, the transfusion of blood would seem to be a logical procedure.

(*a*) *Secondary to Severe Infections.* There were three such cases. The first was a case of hemorrhagic disease of the newborn in a child whose mother had breast abscesses. The immediate result of the transfusion was brilliant. The hemorrhages stopped at once and the temperature dropped. After the transfusion, however, the temperature gradually rose again, ear suppuration set in and bleeding recurred from the mouth, skin, and intestines. The hemorrhages now were very slight and the child died of infection, not of hemorrhage.[12]

The second was a case of gonorrheal rheumatism with very severe hemorrhagic disease. The blood culture was negative, and

it is not absolutely certain that the purpura was secondary to the gonorrhea. The patient's general condition which had been steadily getting worse before the transfusion, commenced to improve almost at once after it. There continued, however, to be some new hemorrhages, joint pains, etc., for about a week. The general clinical course of the disease was abruptly changed by the transfusion, and the patient ultimately recovered.

The third was a case of hemorrhagic diphtheria.[13] After the transfusion the bleeding from the nose stopped and petechiæ no longer appeared, but the toxic symptoms due to the diphtheria continued, and the patient died one week later.

It is apparent, then, that in hemorrhages secondary to infections transfusion may check the hemorrhage, but that, of course, the ultimate result will depend upon whether the body overcomes the infection.

(*b*) *Secondary to Leukemia or Pernicious Anemia.* The results in leukemia in general will be discussed below, but there were 4 cases of lymphatic leukemia in which the indication for transfusion was hemorrhage from the mucous membranes. In 3 of these cases the leukemia was acute and the hemorrhages were uninfluenced by transfusion. In the fourth case the leukemia was of the chronic type, and the hemorrhages, which had not been so severe as in the other 3 cases, stopped after transfusion.

The case of pernicious anemia was one in which the hemorrhagic tendency only appeared when the leukopenia became marked (between 950 and 3000 leukocytes per cubic millimeter). Transfusion had little effect.

Aside from these cases it is possible that a peculiar form of purpura fulminans in which the polynuclear leukocytes are so greatly diminished as to almost disappear while the lymphocytes in the blood remain approximately normal or increase, is really a form of sublymphemic leukemia (perhaps better called leukopenic lymphemia). We have observed several such cases. One of them was one of the fatal cases described above under the heading of Idiopathic Purpura.

(*c*) *Secondary to Jaundice.* There were thirteen transfusions in 12 cases of prolonged obstructive jaundice. Of these cases 4

were transfused preliminary to operation to prevent hemorrhage, 7 were transfused for persistent hemorrhage after operation, and 1 was transfused simply to improve the general condition. Of the 4 cases transfused to prevent postoperative hemorrhage, such hemorrhage occurred, nevertheless, in 1. In this case a fatal intraperitoneal hemorrhage took place. Of the others, 1 died three days after laparotomy with symptoms of cholemia; the third stood the exploratory laparotomy well and died three months later. All of the 3 cases proved at the operation or autopsy to be cases of malignant disease.

The fourth case of transfusion preliminary to operation was a case of obstructive jaundice due to stone in the common duct, in which hemorrhages from the intestine leading to a marked anemia occurred before any operation was attempted. No further hemorrhages occurred after transfusion, and a successful operation was done. This was the only case in the twelve transfused for jaundice, which ultimately recovered.

Of the 7 cases of obstructive jaundice with persistent postoperative hemorrhage, 4 were due to stone or inflammation, 3 were cases of malignant disease. In all 4 of the non-malignant cases, hemorrhage from the wound continued after the transfusion as before.[14] Of the 3 malignant cases, 1 was improved by the transfusion. There were no further hemorrhages, and the patient left the hospital relieved. The second was a case in which there was an almost fatal hemorrhage from the gums and the wound two weeks after operation, with repeated small hemorrhages continuing. Transfusion, only done a month after the operation, greatly improved the patient's general condition. Repeated small hemorrhages continued, but the patient lived for three months after transfusion. In the third case gastric hemorrhage continued unchecked by the transfusion and the patient died.

Postoperative hemorrhage due to cholemia was checked then completely in only 1 case, partly in 1 other, and not at all in 5 cases. Furthermore, the precautionary transfusion before operation failed to prevent the dreaded postoperative hemorrhage in 1 of the 4 cases in which it was tried. These results are disappointing and require explanation.

The exact cause of the hemorrhagic tendency in jaundice is still a matter of dispute, but undoubtedly the changes in the viscera as well as in the blood resulting from the prolonged toxic action must be profound. One can hardly expect these changes to stop at once even after successful operation; and it would seem that the value of the transfused blood is impaired by the same toxic agencies which have already injured the patient's blood. If better results are to be obtained in these cases we shall probably have to adopt the rather bold course of a preliminary blood-letting followed by a large transfusion (two donors), so as to replace as much as possible of the patient's blood. If this is not done before operation, preparations should be made before operation so that in case of hemorrhage it can be done at the earliest moment. And finally transfusions should be repeated, if necessary.

IV. Transfusions for Blood Diseases. 1. *Pernicious Anemia.* There is no question connected with transfusion that has aroused more interest than that of the value of transfusion in pernicious anemia. The experiences of different observers have varied widely; while some have reported brilliant results others have condemned transfusion as useless or even harmful. With an experience of thirty-five transfusions in 25 cases of undoubted pernicious anemia we have been able to reach certain definite conclusions. (We are excluding from consideration 3 cases in which the diagnosis of pernicious anemia was not certain, 2 of which made apparent cures).

In the 25 definite cases there were no cures; 14 of them underwent more or less prolonged remissions immediately following transfusion, while 11 of them showed little or no effect.

Of the 11 which showed little effect, 3 were moribund at the time of transfusion and died within a few hours or days. The other 8, in spite of marked rise of hemoglobin and temporary symptomatic improvement, showed no interruption in the course of the disease but continued to destroy their blood at about the same rate as before transfusion.

Of the 14 patients who showed progressive improvement following one or more transfusions, 1 had a remission lasting approximately three months, 3 had remissions lasting six or more months, 3 lasting a year or more, and 3 lasting over two years; 8 of the

patients are alive, 3 of them less than three months, the others respectively six months, nine months, one and a half years, two and three-quarter years, and four years since the first transfusion. Of these all are in a remission stage. We believe that our results would have been still better had we been in a position to have the transfusions repeated whenever the hemoglobin began to drop.

Two patients underwent splenectomy subsequent to transfusion. In one of these the splenectomy was done after the patient had left our hands, and we only know that in general the splenectomy had little effect and the patient died a few months after it. The second was a remarkable case, already reported by Dr. Buerger.[15] In this case the first transfusion done over three years ago, at a time when the patient seemed in an almost hopeless condition (hemoglobin 18 per cent., general anasarca), was followed by a remission lasting a year, during which the patient was practically in perfect health but showed the blood picture typical of pernicious anemia remissions. Then the anemia gradually progressed again, and a year and a half after the first a second transfusion was done. The patient only held this blood for a few weeks and then again gradually became anemic, so that after three months the hemoglobin was 26 per cent. A third transfusion now raised the hemoglobin to 35 per cent., and a week later, when the hemoglobin had risen to 53 per cent., a splenectomy was done.

Since the splenectomy, the patient has been in a remission stage and she is now in excellent health. The examination of the blood on March 15, 1915, showed the following: Hemoglobin, 102 per cent.; erythrocytes, 3,660,000; leukocytes 9500; polynuclear neutrophiles, 53 per cent.; lymphocytes, 43 per cent.; mononuclears, 2 per cent.; eosinophiles, 2 per cent.; no nucleated erythrocytes or Jolly bodies;[16] undoubted tendency to macrocytosis.

Transfusion, then, so far as our experience goes, is never curative in pernicious anemia. It is a symptomatic remedy which with greater certainty than any other known remedy overcomes the chief symptom of the disease—the anemia. But it does more than this; in about half the cases it initiates a remission. It is true that remissions occur even in the most desperate-seeming cases without transfusion. But the promptness with which the remission occurred

in 14 of our cases leaves no doubt that the transfusion stimulated the remission.

It is well known, of course, that cases of pernicious anemia often pass early in the disease through one or two blood crises in which marked anemia is followed by a striking remission. And it might be thought that those cases in which transfusion was followed by a remission were such early cases, and that the transfusion merely coincided with the blood crisis. But an investigation of the histories of the cases shows exactly the opposite to have been the case. The cases which improved after transfusion were mostly cases which had already run a rather long course and gone through one or two crises, while the cases which failed to improve were for the most part cases of short duration. Of 12 cases whose previous histories could be fairly accurately ascertained and which showed remissions after transfusion, the average duration of the disease before transfusion was nineteen months, whereas of 8 similar cases which failed to show a remission the average previous duration was only ten months (Table I).

Table I.—Duration Before Transfusion of Cases in Which Transfusion was Followed by

Remission.		No remission.	
Case No. O. S. 18	3 years.	Case No. O. S. 53	6 months.
" No. O. S. 43	3 years.	" No. O. S. 60	6 months.
" No. O. S. 87	3 months.	" No. O. S. 85	6 months.
" No. N. S. 1	1½ years.	" No. N. S. 35	2 years.
" No. N. S. 9	8 months.	" No. N. S. 53	9 months.
" No. N. S. 22	2 years.	" No. N. S. 54	3 months.
" No. N. S. 42	2 years.	" No. N. S. 78	2 months.
" No. N. S. 66	6 months.	" No. N. S. 99	2 years.
" No. N. S. 83	1 year.	(First transfusion.)	
" No. N. S. 91	1 year.		
" No. N. S. 93	3 years.		
" No. N. S. 99	2 years.		
(Second transfusion.)			

From this we can roughly divide pernicious anemia cases into two groups: (1) chronic cases which tend to undergo remissions spontaneously and in which new remissions can be brought about by transfusion, and (2) virulent, rapidly progressive cases in which transfusion has little effect.

Aside from this we cannot say what factors determine whether a given transfusion will produce a remission or not. The size of

the transfusion is not the deciding factor because remissions occurred after small as well as after large transfusions. Compatibility of the blood, in the ordinary sense, plays no role, as hemolysis and agglutination were most carefully excluded in all but 1 of our cases (this case died eight hours after transfusion). There are probably other not yet recognized differences between the bloods of donors, and we would suggest that if a remission occurs after a first transfusion an effort be made to obtain the same donor when another transfusion becomes necessary for the patient, whereas if no remission occurs a different donor ought to be tried. *In 2 of our cases in which a first transfusion failed to produce a remission a second transfusion from a different donor did so.*

It is possible that the degree of anemia which is reached before transfusion is resorted to may have something to do with determining a remission. The average hemoglobin percentage, before transfusion, of the 14 cases which showed remissions was 27 per cent., whereas the average of 9 cases which showed no remissions (excluding the 3 rapidly fatal cases) was only 20 per cent. In the former group there were 6 cases with hemoglobin of 30 per cent. or over, while in the latter there were only 2 cases in which the hemoglobin was as high as 30 per cent. This is, however, not an invariable rule, as 4 of the remission cases had low percentages (10, 13, 15, and 16 per cent. respectively) before transfusion. This observation should, nevertheless, certainly lead us to abandon our present timid habit of waiting until an extreme grade of anemia is reached before transfusing these cases.

This conclusion is further supported by another consideration. Anemia itself leads to disturbed functions or actual degenerations of viscera. Thus the persistence of a grave anemia hinders recovery from any disease, including anemia, while the mere temporary relief of anemia tends to break the vicious circle.

The effect of the transfusion on the general condition of patients with pernicious anemia is very often striking. The appetite usually improves rapidly and mental disturbances are apt to clear up. As far as our experience goes the glossitis is not directly influenced nor are, as a rule, the symptoms indicative of spinal cord involvement (except as regards the feeling of weakness which may improve

with the increased feeling of strength in the entire body). In 2 cases in which we studied the gastric secretion after transfusion the achylia persisted, although the appetite and the subjective gastric symptoms improved greatly. In our last case we found that the systolic murmurs heard over the heart disappeared when the remission following transfusion was well established.

Of particular interest is the influence of transfusion on the fever, which is such a conspicuous feature of a large number of cases of pernicious anemia. It has been found in over 60 per cent. of the cases (in one report as high as 80). In 5 of the 6 febrile cases which we investigated the fever disappeared after transfusion. This phenomenon is not peculiar to this form of anemia, for among 16 other cases of anemia due to a variety of causes (excluding infections), febrile before transfusion, 8 became afebrile after it. (These included cases of gastric hemorrhage, hemophilia, splenomegaly, uterine hemorrhage, purpura, etc.). These observations lend strong support to the view that there exists a fever dependent upon anemia as such, the so-called "anemic fever."

We have in transfusion a means of determining in pernicious anemia (and probably in some other conditions) which symptoms are due to the poison of the disease and which to the anemia that is one of the results of the poison.

We may summarize our conclusions with regard to pernicious anemia as follows: *Transfusion is the best remedy for pernicious anemia; it never cures, but it leads to remissions in about half the cases;* it may repeatedly lead to remissions, but the duration of the later remissions is usually shorter than of the early ones. This is possibly due to the mere exhausting effects of protracted anemia itself. For this reason we believe that transfusion should be resorted to early instead of late, and that it should be persistently repeated as often as is necessary to keep the patient from developing a marked grade of anemia.

With regard to splenectomy, we believe from the experience up to the present time that it should be done when remissions of good duration are no longer (or not at all) obtained by means of transfusion. It may, of course, be necessary to transfuse before splenectomy if the patient is in a precarious condition. It is advisable that

in patients who have been splenectomized and have had no remission, or who relapse, transfusions be tried. In this way we will learn whether the patient's life is more prolonged by initial splenectomy and later transfusions, or *vice versa*.

2. *Leukemia*. There were transfusions in 10 cases of leukemia, 9 of the lymphatic, 1 of the myeloid type; 4 of the cases were of the acute variety, with large lymphocytes predominating. In 3 of these the transfusions were without effect and the patients died in a few days. In the fourth the patient's life was probably prolonged for three months by two transfusions. In these cases there were no significant changes in the blood-picture following transfusion.

Of the 5 cases of chronic lymphatic leukemia 1 showed little change in the blood or in the clinical condition the other 4 showed along with some clinical improvement interesting changes in the blood-picture.

The first case was remarkable. It was a typical case of chronic lymphatic leukemia of a year's duration, showing, besides enlargement of the spleen and lymph nodes, peculiar skin infiltrations. The white cells numbered 120,000 and the lymphocytes 85 per cent. Simultaneous with transfusion a phlebotomy of fifty-five ounces was performed by Dr. Harold Neuhof (to whom we are indebted for the use of his notes). A month after transfusion the leukocytic blood count had become practically normal, and it remained so until the patient's death, one year later. The skin infiltrations, splenic and lymph-node enlargements, diminished for about two months, then returned, and the skin lesions developed into large tumors of the appearance of mycosis fungoides (a condition which resembles leukemic cutaneous lesions). These progressed and caused death. We are at a loss to explain the permanent change in the blood picture; it could hardly have been due to the Roentgen-ray treatment which was given from time to time.

The other 3 cases also showed marked change toward the normal, or for a time actually normal leukocytic blood pictures, but in all of them the leukemic blood picture ultimately returned. In the second case this change was least marked; the leukocytes, which had been 10,000 with 5 per cent. polynuclear cells and 95 per cent.

lymphocytes before transfusion, became 4500, with 30 per cent. polynuclears the next day, but in a week had returned to about the same as before transfusion.

The third patient showed a gradual change. Two days after transfusion the leukocytes had decreased from 140,000 to 66,000 and the polynuclears increased from 18 to 35 per cent. This steadily progressed until two and a half months later, when the total and differential leukocyte count was entirely normal. During this time the treatment carried on by Dr. Alfred Meyer, consisted of frequent intramuscular injections of ascitic fluid. The leukocytic blood picture remained normal (in spite of progressing anemia) for another month; then the leukemic blood type gradually returned and the patient died four and a half months after transfusion.

In the fourth case an extreme leukemic blood-picture gradually became normal a week after transfusion (concomitant with striking clinical improvement). The leukocyte picture persisted normal for a week, and then in a few days became typically leukemic again. In the one case of myeloid leukemia there was no effect on either blood picture or clinical course.

Contrary to our expectation we find, then, that transfusion does exert an influence on chronic lymphatic leukemia. The blood counts in these cases were repeatedly made, and were confirmed by several men, so that there is no possibility of error. It is true that the patients were receiving the other usual forms of treatment, but so were they before transfusion; and everyone knows how rare it is for cases of lymphatic leukemia to get a quantitatively and qualitatively normal leukocyte picture under treatment. In one of the 4 cases which showed a change it was transient and partial, and appeared immediately after transfusion. In the other 3 it appeared gradually during one or more weeks after transfusion and lasted one week in 1 case, about two months in another, and a year (until death) in a third.

It should be remembered that all these cases received only one transfusion, and that the greatest result was obtained in the case which had a rather large phlebotomy simultaneous with transfusion. We believe, therefore, that in some obscure way normal blood has an effect, and that the results of transfusion are good

enough to warrant its further trial in chronic lymphatic leukemia. Such a trial should consist not of single but of systematically repeated transfusions, and we would suggest a preliminary or simultaneous phlebotomy as was done by Dr. Neuhof in his case.

V. Transfusions for Infectious Diseases. The idea of transfusion for infectious disease is almost as old as transfusion itself. Aside from the control of hemorrhage (in those cases complicated by hemorrhages), transfusion may be of use in infections, either for its general strengthening effect (particularly in protracted cases) or for some specific effect of the transfused blood. Normal blood usually has less specific bactericidal power than the blood of the infected individual, and for this reason the transfusion of normal blood probably helps only in the former way (general support). But the blood of persons who have recovered from an infectious disease or who have been artificially immunized has specific properties not only in the antibodies of the plasma but possibly also in the cells. For there is every reason to believe that in those diseases immunity to which is cellular rather than humoral the blood cells share the immune powers of the other body cells. And in this regard human blood offers the great advantage over animals' immune sera—that the blood cells transfused continue to live and functionate. Not enough attention has been paid to this possibility. We have made a small beginning in attempting to immunize a donor to the endocarditis coccus (Streptococcus viridans or mitis) before transfusion; but unfortunately most of the transfusions which we can report in infections represent haphazard trials in forlorn cases. Systematic attempts in this direction may be richly rewarded. Particularly in those diseases recovery from which confers lasting immunity, like typhoid fever, scarlet fever, and the other exanthemata, hospitals should endeavor to secure the consent of recovered patients to return and act as donors.

Aside from the typhoid fever cases (discussed above under hemorrhage in typhoid fever, and the cases of purpura complicating infectious diseases (discussed under Hemorrhagic Conditions, page 13), we can report on transfusions in 10 cases of infection with pyogenic organisms and in 4 cases of subacute streptococcus endocarditis.

1. *Infection with Pyogenic Organisms.* Of the 10 cases, 6 were due to the Staphylococcus aureus, 2 to general infection by streptococci, and in 2 the infecting organisms were not determined. All were in the most desperate possible condition at the time of transfusion, and the 4 that recovered probably owe their recovery to the transfusion.

The 2 cases in which the organisms were not ascertained were both uterine infections, the one an infected abortion, the other a case of multiple infections (so-called pyemia) following a pelvic abscess. In both transfusion had no effect.

Of the 6 cases due to the Staphylococcus aureus, 4 were cases of osteomyelitis of the femur; 2 of these recovered; 2 were cases of multiple infections (pyemia) with bone abscesses, and 1 of these recovered. All 6 cases had been ill for two months or more and were very anemic (all but 1 had a hemoglobin percentage of approximately 30 per cent.). The 3 cases that died succumbed a few days after transfusion, and indeed were moribund at the time; 1 of them died of acute hemorrhage from an eroded artery. Of the 3 cases that recovered, all had been steadily growing worse before transfusion and promptly commenced to get well after it. The effect was unmistakable, and leaves no doubt that in prolonged suppuration mere anemia and exhaustion may be all that prevent the overcoming of infection. In such cases transfusion of normal blood may offer an almost specific cure.

Of the 2 cases of general streptococcus infection, the 1 which died was practically hopeless from the start, a Ludwig's angina with multiple abscesses, complicating diabetes. The 1 which recovered was a case of (apparently) terminal streptococcus blood invasion from an unknown source, complicating a remarkably prolonged typhoid fever. (This case has already been referred to under the heading of Typhoid Fever.) In this case also it was the mere exhaustion due to prolonged fever that allowed the secondary invader to enter the blood, and the recovery after transfusion was prompt and complete.

In prolonged infection, then (due attention having been paid to surgical needs), the transfusion of normal blood may be extremely valuable and should not be too long delayed. In acute infections

the value of transfusion should be determined by more extensive studies than have hitherto been made.

2. *Endocarditis.* There were transfusions in 4 cases of subacute endocarditis due to the endocarditis coccus (Streptococcus viridans, Streptococcus mitis), 1 case being in the bacteria-free stage.[17] In the 3 active cases the transfusions were done in the hope of combating the anemia and of helping the patient fight the infection. In the bacteria-free case the object was the relief of a profound anemia.

In the first case two transfusions were done. At the time the first was done the hemoglobin was 39 per cent. The hemoglobin was raised to 55 per cent. and the next day was somewhat over 60. The general condition improved remarkably, but the temperature kept up as before, and the cocci were found in the blood repeatedly. The hemoglobin did not drop to the original figure for four months, a remarkable result, because in such cases, when not transfused, once the anemia begins it becomes progressive. A second transfusion was done, using a donor who had been treated with a vaccine made from the organism present in the blood of the patient. This transfusion relieved the anemia, but the patient died a short time later from cerebral symptoms interpreted as being due to the rupture of an embolic aneurysm.

There were two further observations made in this case that are of sufficient importance to mention here. Bactericidal studies were made of the serum of the patient and of the serum of the second donor. They were both moderately bactericidal, as was the mixture of the two. The full blood of each was also moderately bactericidal, but the combination of both full bloods was completely bactericidal. This shows that serum studies are insufficient. One should also study the plasma and the full blood if one wishes to obtain correct estimates in making bactericidal studies.

The other observation relates to a severe pain that the patient referred to the right orbit, and which disappeared promptly after the first transfusion. It did not return until the hemoglobin again was reduced to the early low figure. We were evidently dealing with an anemic neuralgia. This observation is, as far as we know, unique.

In the second case there was some improvement in the general condition, but only for a few days. The case was a very advanced one.

The third case was the only case in our entire series of a fatal accident following transfusion (aside from the two agglutinative and hemolytic transfusions discussed elsewhere[18]). A large transfusion was done and no track was kept of the hemoglobin (it was one of the early cases). At the end of the transfusion the patient suddenly showed all the signs of acute cardiac dilatation, and died a few hours later. Autopsy revealed not only extensive aortic and mitral vegetations and an unexpected tuberculosis of the lungs, but extensive miliary necroses of the heart muscle. It has never been entirely clear whether death was due to liberation of toxic substances by some lytic action of the introduced blood on the circulating bacteria or to mere mechanical dilatation of the already damaged heart muscle. The latter possibility, however, seems far more likely. Excessive transfusion is an accident which can now be easily avoided by the method of calculation which we have introduced[19] even when the transfusion is a direct one (artery to vein). Particularly in cases of cardiac disease should the amount to be transfused be carefully calculated.

The fourth case of endocarditis to be transfused was a man who had for some time been in the bacteria-free stage of the disease and who was suffering from anemia. The hemoglobin was 20 per cent., and the patient showed moderate general edema and marked edema of the feet and legs. He was put on the Karrel diet for a couple of days so that the addition of the transfused blood should not overburden his heart. The change in his condition after transfusion was very pronounced. Before the transfusion he had no appetite, suffered from insomnia, and had marked dyspnea even when walking on the level. After the transfusion his appetite returned, he slept well, felt much stronger, and was able to walk up four flights of stairs with only moderate discomfort. His dyspnea on exertion had evidently been due much more to his anemia than to his valvular disease. He eventually became anemic again and succumbed to his disease.

As to the advisability of performing transfusions in these endo-

carditis cases, we believe that they are worth trying so as to help keep the patient alive for a longer time, and so as to put the organs into better condition to respond to any methods of therapy that are tried. We believe in such cases it is advisable to test the value of repeated transfusions, especially because we now know that there is a tendency for them to become spontaneously bacteria-free.

VI. Transfusions for Intoxications. 1. *Acute Poisoning.* In severe intoxications transfusion would only seem to be indicated if a considerable part of the poison is contained in or has acted on the blood. Among poisons which act in this way are carbon monoxide, hydrocyanic acid, benzol, nitrobenzol, and possibly carbolic acid. In such cases, of course, a large phlebotomy must be done before or during the transfusion.

In illuminating gas poisoning, transfusion is now accepted as the best treatment. We have seen 1 case of poisoning by illuminating gas combined with a large dose of morphin. In this case the patient recovered after the letting of a pint of blood, a large transfusion, and artificial respiration for about three hours (part of the time by Meltzer's intratracheal insufflation).

In a case of poisoning by a large dose of morphin with an unknown but probably small dose of prussic acid the same measures failed to save the patient. However, he did have a temporary return of consciousness after (although not immediately after) transfusion.

2. *Diabetic Coma.* Four cases of diabetes were transfused. The idea of trying transfusion for the relief of diabetic coma occurred to Dr. Elsberg, and the first case was transfused by him. Temporary improvement of an impending coma occurred, but three days later all the symptoms returned and the patient died. A similar result was obtained in two other cases of diabetic coma, the one complicated by a carbuncle, the other complicated by gangrene of the foot. In neither of these cases was there more than transient effect on the coma.

Transfusion was also performed in a case of diabetes complicated by pernicious anemia in a young woman.[20] Two transfusions were done in this case, each time with a marked effect on the anemia, but none on the glycosuria or the occurrence of acetone and diacetic acid in the urine. The patient subsequently died of the pernicious anemia, which was of the rapidly progressive type.

Transfusion then had no effect on diabetic coma or on the course of a severe diabetes.

VII. Transfusions for Debilitated Conditions. Now that transfusion has become a relatively easy and perfectly safe procedure, it can be applied to the relief of anemia from all sorts of causes. In cancer there is no reason to expect real benefit from it except in connection with a radical operation. A number of the cases described above under the heading Transfusions Preliminary to Operation, were such cases, and were very successful. In other wasting diseases, such as tuberculosis, transfusion may be indicated to relieve anemia and improve the general resistance of the patient.

There are many cases of simple anemia due to malnutrition or to minor causes or to no assignable cause. In some of these cases ordinary treatment is unsatisfactory or too slow, and transfusion would seem to be justified. In 2 such cases, the one anemic from no definite cause, the other as a result of repeated small losses of blood from hemorrhoids, transfusions were done with most satisfactory result.

Part III.

Notes on the General Management of Transfusions.

1. *Dangers and Complications of Transfusion.* Is transfusion dangerous to the patient? The idea is still widely prevalent that it is; and yet we believe that to-day transfusion has become one of the most certain and safe of procedures. The three classes of accidents that formerly were feared—those due to incompatible blood, to dilatation of the heart, and to introduction of air—are all easily preventable by taking suitable precautions.

Accidents due to incompatibility of blood, that is to say, to hemolysis or agglutination of the red blood cells of either donor or patient by the serum of the other, have been fully discussed in a previous article by Ottenberg and Kaliski.[21] Hemolysis is by far the greater danger and was found both clinically and experimentally[22] to show accurate correspondence between the test-tube phenomenon and the occurrence in the body. *In no case in our series in which hemolysis or agglutination did not occur in the test tube were any untoward*

symptoms observed which could be attributed to these phenomena. There were 3 cases in which agglutination of the donor's red blood cells by the patient's serum was observed in the test tube. Two of these patients died shortly after transfusion, and in the blood smears of both of them phagocytosis of red blood cells by leukocytes was observed. In the of these cases agglutination was the only test-tube phenomenon, in the other hemolysis as well as agglutination. In the third case the patient's serum was hemolytic to the donor's cells, and an extensive hemoglobinuria occurred after the transfusion, from which, nevertheless, the patient recovered. There was a fourth case, an emergency in which no tests whatever were made (a brother being taken as donor), and in which the patient died with convulsions during the transfusion. The patient, however, was already in bad condition (hemorrhage following nephrotomy for calculus), and it is not certain whether death was due to transfusion or not. It seems probable that it was, however, as the fatal transfusion was the second one in this case, and at the first transfusion much difficulty had occurred in finding a donor because the patient's serum was powerfully hemolytic to the blood cells of most of the donors examined.

The instances in which the donor's serum is agglutinative toward the patient's cells have been shown by one of us[23] to be theoretically far less dangerous; and, in fact, we have seen five transfusions of this kind in none of which were there any untoward symptoms or any phagocytosis in the circulating blood. We have been able to avoid transfusions in which the donor's serum was hemolyticto the patient's cells. In the great majority of cases it is possible by examining five or six different people to find one whose blood is entirely compatible with the patient's. Twice in our experience transfusion has been given up because the patient's serum was found to be powerfully hemolytic to the cells of every donor examined. In one of these instances, however, only a few donors were examined, and it is likely that if a large number could have been examined a suitable donor could have been found.

We feel absolute confidence, then, that if the tests have been carefully done nothing whatever need be feared from this source. It is needless to say that these tests require expert work and a well-

equipped laboratory. They take about three hours to perform, and should never be omitted except in the most urgent cases.

The danger due to dilatation of the heart depends not only on the condition of the patient's circulation but on the amount of blood transfused and the rate at which it is delivered. When the patient's heart is known to be embarrassed, transfusion should be interrupted every few minutes. *The amount of blood to be transfused should be decided on before each transfusion* according to the principles we will discuss below. In can be controlled during a syringe transfusion by direct measurement and during a direct transfusion by the method of calculation which we have introduced.

We have twice seen hypertransfusions. The first case was the rapidly fatal case described above under the heading of Endocarditis. The second case was a case of pernicious anemia in which a large transfusion was performed, the hemoglobin being raised from 15 to 52 per cent. During the transfusion the patient developed all the signs of a pulmonary edema with nausea and vomiting. On the day following there was generalized edema with continued pulmonary edema and hematuria. On the third day the patient developed jaundice. She gradually recovered from these urgent symptoms, but the rapid blood destruction which had been going on continued, and she died three weeks later.

Slight jaundice occurred in 2 other cases. The one was probably an instance of Banti's disease (one of our early cases; incomplete records were kept of the case, so that it was not included in the tabulation of the present series). We believe that the jaundice was probably due to the same cause (excessive transfusion) possibly accentuated by the special hemolytic tendency of the disease itself. In the other case in which a slight jaundice followed transfusion the patient was suffering with a carcinoma of the stomach with numerous metastases.

Hematuria also occurred in 1 other case. It was a case of nephritis with uremia and anasarca. This case was not discussed above under the subject Indications for Transfusions. A phlebotomy of 400 cubic centimeters was followed by a very large vein-to-vein transfusion. It was impossible to follow the amount of blood being transfused by the calculation method because

the patient's and donor's hemoglobin were practically the same at the start. Transient hematuria occurred which may have been due to excessive transfusion, but more likely to a special permeability of the kidneys from nephritis, since red cells were found in the urine also at other times independent of the transfusion.

Aside from these unfavorable reactions due to incompatible blood or to hypertransfusion, a more or less marked febrile reaction occurred in about 10 per cent. of all our cases, and skin eruptions, usually urticarial in character, occasionally a few petechiæ, appeared in another 10 per cent. In no instance were these symptoms serious, and in every case they cleared up within three days.

2. *The Donor.* The securing of donors always offers a certain amount of difficulty on account of the necessity of examining a number of men in order to be certain to find someone whose blood is compatible with that of the patient. We have generally inserted an advertisement in the newspapers. Occasionally relatives of the patient have been used, but, as has been shown elsewhere,[24] it is quite as necessary to make the blood tests of relatives as of strangers. In New York there is never any lack of response to advertisements, and we make a practice of keeping a reserve list of men who have answered such advertisements and who can be reached by telephone or otherwise, for use in emergency transfusions. The applicants never object to the taking of about 5 c.c. of blood for hemolysis tests and Wassermann reaction. Sometimes a small stipend is given to them for allowing this to be done.

It is important to know what to tell donors and what can be promised them. They can freely be promised absolute safety and a minimum of pain. When a syringe transfusion is to be done they are able to go to work again the next day. When a direct transfusion is done the wound hampers work for a week or two and in these cases the amount of money paid the donors is usually larger. We have only once known the donor to have any subsequent trouble from transfusion. This was due to an infection of the wound, caused by his own carelessness. In the great majority of instances the recovery of the lost blood by the donor after transfusion is surprisingly rapid, and several donors have been in perfect health and have been used again for transfusion a month or six

weeks after the first transfusion. *It is wise in every instance to have the donor before the transfusion sign a legal form, relieving the patient and the surgeon from further liability, and stating the amount of money that he is to receive.*

Aside from the blood test a physical examination should be made to rule out infectious disease (especially tuberculosis and syphilis) or any cardiac condition which would contra-indicate the use of a particular donor. The physical build and temperament of donors are to be taken into consideration. Large men (weighing one hundred and sixty-five pounds or over) are to be preferred, as more blood can be taken from them with safety. Very fat men are not desirable, because in proportion to their weight their blood volume is less. Men of nervous or timid temperament should not be taken, as their actions are likely to interfere with the success of the transfusion. For syringe transfusions the character of the superficial veins is important.

The watching of the donor during transfusion is more important in direct than in syringe transfusions. The donor should be given fluids, such as soup and hot coffee, but whisky should be avoided, as it frequently causes vomiting and does not seem to do any good. The actions of different men during the loss of blood is exceedingly variable, and for this reason the observation of the donor is not a very reliable guide in transfusion. The pulse more frequently becomes slow than rapid. Toward the end of the transfusion it usually becomes soft, sometimes dicrotic. If the pulse rate becomes less than sixty it is best to stop the transfusion. Often the appearance of the patient is unchanged until a sudden collapse occurs. Sometimes repeated yawning occurs toward the end of the transfusion, as an indication that enough blood has been taken. The first signs of collapse are sweating and pallor, and when these occur a real collapse almost invariably follows, with thready or imperceptible pulse, semiconsciousness, and vomiting. Recovery usually takes place without any special stimulation. We have only once seen a severe collapse that required active steps to be taken. This was a transfusion in a case of shock due to typhoid perforation in which an unusually large transfusion was done, and on account of the patient's desperate condition little attention could be paid to

the donor. However, with stimulation the donor recovered in about a half-hour and had no further trouble. In a number of instances large amounts of blood (three pounds or more) are known by actual weighings to have been transfused without causing serious trouble.[25]

If sufficiently long periods are allowed for the hemoglobin percentage to reach the normal again the same donor can be used for repeated transfusions, and there are certain advantages in doing this.

3. *The Technic of Transfusion.* What is the best method of performing transfusion? This is not the proper place to enter into an extended discussion of questions of technic, but since the technic often plays a very important part in determining whether a transfusion should be done or not we will briefly consider the advantages of the several methods. The syringe method, as practised by Lindeman, possesses great advantages over other methods. It involves no trauma and very little pain, and thus does not add the shock of a surgical procedure to the burden of an already sick patient. The exact amount transfused is always known. Not the least advantage is that syringe transfusions can be done repeatedly on the same patient as often as desired. This opens all sorts of new possibilities in transfusion therapy. To some it will appear to be a disadvantage that the syringe method requires a more expensive apparatus. This, however, is no real obstacle. The aspiration of blood from the donor should not be left to an untrained assistant, as this part of the procedure is quite as difficult as the injection into the patient.

The disadvantage of the direct transfusion is that it is a cutting operation and destroys a vein of the patient, so that only a limited number of repeated transfusions can be done. When the patient does not have a low percentage of hemoglobin at the start of the transfusion it also has the disadvantage that one cannot estimate how much blood is being transfused. We believe that those undertaking to do transfusions should be skilled not only in the use of the syringe method, but also in the direct method conducted by means of the Elsberg cannula or Carrel suture. It may be necessary at times to use one of the latter methods.

We have had no experience in the use of anticoagulants, such as

hirudin and sodium citrate. In hemorrhagic diseases, which constitute so important a part of the indications for transfusion, such anticoagulants would seem to be contra-indicated. Dr. Richard Lewisohn (personal communication) has made studies of the value of hirudin added to the blood to be transfused and finds it to be not harmless.[26] There are reports that sodium citrate can be used without danger. The method of defibrination is open to the same objection in hemorrhagic conditions as the use of anticoagulants—namely, that it removes fibrinogen and blood platelets. Moreover, it is impossible to defibrinate blood without mechanically injuring the red blood cells to a certain degree, and there is a possibility that if a large amount of defibrinated blood is transfused the antithrombin of the patient's blood will not be sufficient to neutralize the action of the thrombin in the defibrinated blood and that intravascular clotting will occur.

In the great majority of the transfusions reported in the present paper the direct method—artery-to-vein or vein-to-vein—was used. In about twenty of the later transfusions the syringe method was used.

4. *Amount of Blood to be Transfused.* The quantity of blood to be transferred should always be determined beforehand by consideration of the following data:

(*a*) The weight of the donor.
(*b*) The weight of the patient.
(*c*) The condition of the patient.
(*d*) The nature of the disease.

The first two factors have been discussed by us in a previous paper.[27] The third has been considered above under Dangers in Transfusion. As far as the nature of the disease influences transfusion the following conditions may be considered:

1. *Hemorrhage.* In hemorrhage an effort should be made so far as possible to replace the lost blood. Experience, however shows that collapse can be overcome and the patient brought into a condition of safety by a smaller amount than has been lost.

2. *Hemorrhagic Diseases.* In hemorrhagic disease a relatively small transfusion (500 c.c. for an adult) is usually enough unless the amount of blood already lost has been very large. In hemorrhages due to cholemia we believe that a large transfusion with perhaps a preliminary phlebotomy is indicated (see Cholemia).

3. *Anemias.* When it seems desirable to raise the hemoglobin to a given point it is important to remember that there is generally a rise of the hemoglobin within twenty-four hours to a percentage somewhat higher than that at the end of the transfusion. We have observed this in the majority of our cases in which there was no hemorrhage after the transfusion. Generally the rise is about 5 per cent., but sometimes it is as high as 10 per cent. It is presumably due to a concentration of the blood. In pernicious anemia a moderate-sized transfusion (500 c.c. to 1000 c.c.) is probably sufficient.

4. *Poisoning.* In the various forms of poisoning, especially in gas poisoning, a large phlebotomy followed by a very large transfusion would seem to be indicated.

5. *Repetition of Transfusion.* As suggested above, there are probably many conditions in which repeated transfusions will accomplish a great deal more than a single large transfusion, or in which the repetition of transfusions may become necessary at later stages of the disease. Some such conditions are pernicious anemia, hemophilia, and infections, whether local or general. There is no danger in repeated transfusions provided the tests for hemolysis and agglutination are carefully done. The likelihood of hemolysis occurring is distinctly greater in the second and third than in the first transfusions, due to the development of immune hemolysins. We have found this experimentally,[28] and several of the cases of fatal hemolysis after transfusion reported in the literature are instances of second transfusions. In 21 of our cases there were two transfusions, and in 3 of them three transfusions, without any special ill effects.

Addendum. Unger[29] has eliminated the difficulties experienced in the Lindeman method by the use of a simple apparatus. Up to the present time his apparatus has been used in twenty cases. Transfusions can be performed very rapidly, 60 c.c. on an average being transferred per minute. Chills, rises of temperature, vomiting and other symptoms that are occasionally seen after transfusions, seem to be less frequent when this method is used than when either the Lindeman or citrate methods are used. We can regard Unger's method as at present the best for direct transfusion.

Hustin,[30] of Brussels, in May, 1914, published animal experiments in which citrate of soda was used and citrate of soda mixed with glucose. He stated that he had successfully used in one human case a mixture of blood and saline solution containing citrate of soda and glucose. He diluted the blood with an equal amount of saline solution because he feared that the 0.2 per cent. strength citrate which he was using in the blood might be dangerous if the blood was not diluted. This method would limit the size of transfusions and apart from that more recent studies have shown that such dilutions and the use of glucose are not necessary. At a meeting at the New York Academy of Medicine at which the present writers communicated some of their studies, Weil stated that he had successfully done transfusions in human beings using a 1 per cent. strength of citrate of soda and transferring amounts of blood up to 250 c.c. The coagulation time of the blood of the patients was not prolonged, in fact shortened.[31] Lewisohn[32] has reported the successful use of citrated blood in large amounts using only 0.2 per cent. of the salt. He feared that the percentage of citrate used by Weil would be toxic when large amounts of blood were transfused.

Weil believes that the great value of the citrate method lies in the fact that the blood may be kept on ice for a number of days and repeated injections of small amounts used. He has done 200 transfusions in 46 cases.[33] He usually injected 300 to 350 c.c. of blood, but in one case he used 1400 c.c. The strength of sodium citrate was 1 per cent., occasionally 0.3 per cent. The blood was used as late as six days after it was obtained, but usually within three days. The reactions after transfusion were unimportant. There was occasionally chilliness and headache. In six cases the temperature rose to 102° F. and in four cases, above 102° F. Polyuria occurred frequently. The patients seemed to hold the blood well. The coagulation time was frequently cut in half very shortly after the transfusion, but returned to the original time within twenty-four hours.[34]

Lewisohn has transferred 25 cases; the highest amount given at one time was 900 c.c., but in one case 1600 c.c. were transfused within twenty-four hours. There was a diuresis in most cases

which stopped within twenty-four hours. Some patients suffered from headache, and some perspired profusely. He has confirmed all of Weil's observations concerning coagulation time. It is important that he has found that the solution can be sterilized without losing any of its value. In three of his cases a chill resulted and in five there was marked temperature reaction. The chills occurred less frequently, however, than they occurred in Lindeman's series.

We have seen all these newer procedures used and believe that the method of Unger and the citrate method are at present the methods of choice. For large transfusions many will prefer the Unger method. The citrate method has distinct advantages when one wishes to make repeated injections of blood. Apart from its great simplicity it will be of particular value when patients live at a distance or when it is desirable that the patient does not realize that an important procedure has become necessary. If future studies demonstrate that citrated blood acts as well in pernicious anemia as uncitrated blood and if no disadvantages are found from its repeated use in cases of hemorrhagic disease, this method will prove the most widely applicable.

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[1] Various parts of this paper were presented at a stated meeting of the New York Academy of Medicine, December 17, 1914, and at the meeting of the Association of American Physicians, May 11, 1915.

[2] Canada Lancet, 1906–07, xl, 1057; Ann. Surg., 1907, xlvi, 329.

[3] Ottenberg and Kaliski, Jour. Amer. Med. Assoc., 1913, lxi, 2138.

[4] Libman and Ottenberg, Jour. Amer. Med. Assoc., 1914, lxx, 764.

[5] Amer. Jour. Dis. Child., 1913, vi, 28; New York Med. Rec., 1912, lxxxi, 979.

[6] We wish to thank the members of the Attending Staff of the Hospital for their generosity in permitting us to utilize the records of the cases that we studied in their services. We are also under obligations to many physicians whose private cases we followed with them.

[7] Repeated small transfusions done by the newer methods would, however, be applicable (see Addendum).

[8] New York Med. Rec., 1912, lxxxi, 979.

[9] See below under Dangers of Transfusion.

[10] Such tests, once performed, would not need to be repeated when the transfusion is done, since the agglutinative property of the blood of certain individuals for the blood cells of certain others are permanent for life, and the hemolytic property which occasionally occurs develops, as a rule, only where there is already agglutinative power present. However, if transfusions are repeated the tests should be repeated also, as we know from experimental work (Ottenberg, Kaliski, and Friedman, loc. cit.) that it is possible to develop immune isohemolysins by repeated direct transfusions.

[11] It is of interest to note that we once saw bleeding stop (case of carcinoma of pancreas, icterus, general hemorrhages) following the use of serum, although the

coagulation time became much longer. The coagulation time is not, therefore, always an index of the bleeding tendency.

[12] This case is fully described by Schwartz and Ottenberg, Amer. Jour. Med. Sci., 1910, cxl, 17.

[13] We are indebted to Dr. Louis Fisher for permission to refer to this case.

[14] One of these cases was transfused twice; in this case the serum of the donor was agglutinative to the patient's blood cells.

[15] New York Surg. Soc., October 2, 1914.

[16] Jolly bodies had, however, been present for a long time after splenectomy.

[17] Libman, Amer Jour. Med. Sci., 1913, cxlvi, 625.

[18] Ottenberg and Kaliski, loc. cit.

[19] Libman and Ottenberg, Jour. Amer. Med. Assoc., 1914, lxx, 764.

[20] We are indebted to Dr. Buerger for permission to use this case.

[21] Loc. cit.

[22] Ottenberg, Kaliski, and Friedman, Jour. Med. Research, 1913, xxviii, 141.

[23] Ottenberg, Jour. Exper. Med., 1911, xiii, 425.

[24] Ottenberg and Kaliski, loc. cit.

[25] Libman and Ottenberg, loc. cit.

[26] Dr. Lewisohn believes that various preparations of hirudin vary in toxicity.

[27] Libman and Ottenberg, loc. cit.

[28] Ottenberg, Kaliski, and Friedman, loc. cit.

[29] Jour. Am. Med. Assn., 1915, lxiv, 582.

[30] Ann. et Bull. de la Soc. Royale de Sci. Méd. et Nat. de Bruxelles, 1914, No. 4, p. 104.

[31] Weil, Med. Rec., New York, January 23, 1915, lxxxvii, 164; see also Jour. Amer. Med. Assn., January 30, 1915, lxiv, 425.

[32] Med. Rec., New York, January 23, 1915, lxxxvii, 141.

[33] These facts were presented by Dr. Weil in a communication made to the American Society for the Advancement of Clinical Investigation, May 10, 1915.

[34] Dr. Lewisohn's publication will appear shortly in the Journal of Surgery, Gynecology and Obstetrics. We are indebted to both Dr. Weil and Dr. Lewisohn for giving us these facts in advance of their publications.

A REVIEW OF THE ADVANCES IN OUR KNOWLEDGE AND TREATMENT OF CANCER IN THE LAST THIRTY YEARS

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But few discussions on the subject of carcinoma have been presented before this Society. The matter is one which has not very greatly interested physicians, for the only treatment available has been operative removal. The recent extensive use of radium and *x*-ray, however, while unfortunately showing that these physical agents have much less therapeutic value than was originally believed, has turned the attention of physicians to the study of the nature and treatment of carcinoma, and I have, therefore, been asked by your President to give a review of the subject for the period since the foundation of the Society in 1885.

It is obvious that only the main facts and but few of the workers in cancer research can even be mentioned in this address, and I shall be compelled to select those whose contributions seem to be the most important, and to disregard entirely the mere details of priority.

In the three decades which have just elapsed the real advances have been due to the introduction of the experimental method, so fruitful in other fields. No important additions have come from the clinical study of human cancer since Virchow laid the foundations and Waldeyer and Thiersch published their fundamental papers. It is true that our understanding of the morphology and classification of tumors has been amplified and the statistical study of large series of operated cases has led to an appreciation of the limits of surgery and the reasons therefor; but no new fact in tumor biology has been discovered by clinicians, though

there are still many gaps which could be filled by careful observation. This review will of necessity, therefore, be confined largely to experimental results.

It has been my feeling that Jensen may be considered the Pasteur of cancer research, for it was he who by a series of painstaking observations first showed the possibility of the continuous transplantation of tumors from one animal to another through repeated generations, although, of course, others before him had published individual cases of successful inoculation. Jensen's first paper (1902) was published in Danish, so that his observations did not become generally known until some time afterward when the main points appeared in a German publication (1903). In this paper he described and illustrated the morphological appearances of tumors in mice; the transplantability of such tumors to other mice of the same race was demonstrated; and it was shown that tumors from albino mice could be transferred to the gray house mice in a small number of cases, but not to the more distantly related field mice, and not at all to animals of other species. He showed, also, that no parasites could be demonstrated, either by stains or by cultural methods, in the tissues of the transplanted tumors. He reported the effects of drying on the cells and their destruction by crushing or by ultra-violet light or by antiseptics, and showed that tumor cells could be kept alive at low temperatures for eighteen days, although they died off rapidly at 37° C. He was the first to call attention to the fact that the growth of the tumor depended upon its vascularization and the necessary connective-tissue reactions which accompany the phenomenon, insisting upon this point as important since it showed that the disease is not an infection, but that the tissues of the host replace the connective-tissue of the original tumor and thus nourish the epithelial cells, which alone are propagated in the body of the new host. All of these points have been repeatedly investigated without in the least invalidating any of Jensen's conclusions. In the same paper, however, Jensen fell into an error by claiming that by the injection of tumor tissue into rabbits he had obtained a serum which had beneficial effects on tumors of mice. Later, he acknowledged that the error was due solely to his lack of knowledge in regard to

spontaneous regression of transplanted tumors in animals. Almost every year since that time this error has been repeated, both by laboratory workers using animals and by clinicians in the treatment of human beings, the most recent instance being the now generally acknowledged failure of Hodenpyl's attempts to cure carcinoma by the injection of serum from a patient with ascites following invasion of the peritoneum by a malignant growth. Even laboratory men do not seem to have learned the lesson that the biological behavior of a transplanted tumor must be accurately determined before therapeutic measures can be tested on it. The numerous reports on the power of diet, drugs, radium, and other agents to induce the disappearance of a tumor are vitiated by disregard of this elementary fact. A number of recent reports have been based upon observations on the Buffalo rat sarcoma, so-called, which has the power of spontaneous regression in various series of from 5 to 40 per cent. Obviously such a tumor should not be used for testing therapeutic agents; only one which grows progressively in from 90 to 100 per cent. of animals will afford reliable data.

About the same time as Jensen, Leo Loeb and Borrel also demonstrated many interesting facts concerning the transplantability of new growths, but the next really important advance was made at the State Institute for the Study of Malignant Disease at Buffalo, under the leadership of Gaylord (1906). It was from this laboratory that the first definite proof was offered that spontaneous regression in transplanted tumors in animals is not infrequent, and that following such regression the animal may be immune to succeeding inoculations. Gaylord also introduced a very useful system of making charts for record, which was improved and extended in Bashford's laboratory, and should be more generally used by those working on this subject, as it offers an admirable means for judging at a glance of the rate of growth and regression of a long series of tumors.

Carcinosarcoma. The genius of Ehrlich and his able assistant Apolant added (1905) the important experimental observation that certain carcinomata of mice may, during growth, produce a sarcomatous alteration in the stroma. Since that time a considerable number of these tumors, still less than a dozen, however, have been

studied and the histological changes have been fairly well determined. It was shown by Haaland in Bashford's laboratory that the sarcomatous and carcinomatous portions could be picked out of sections of the tumor and each propagated separately, retaining the morphological characteristics of the original. Russell in Bashford's laboratory, also, showed that the condition developed usually after a certain period of growth in the carcinoma (some forty to fifty days in the tumors which he studied), and that there was a tendency for the sarcoma ultimately to replace the carcinoma. The importance of these observations lies in the fact that this is one of the few instances in which we are able to watch the origin of a new growth. While it is generally observed that in man the production of a tumor follows chronic irritation only over a very prolonged period, for example, *x*-ray carcinomata usually appear from eight to ten years after the primary injury of the skin, yet here in these small experimental animals the tumor is produced in fifty days. An explanation is not forthcoming. It may be, however, that in the mouse the period of fifty days corresponds to ten years in a human being. Unfortunately, these growths are very rare, and because of the scarcity of material the various interesting and important experiments which have suggested themselves in the last few years have not been possible.

Tumor Immunity. Ehrlich (1906), as a result of his studies on the question of immunity to tumor implantation, brought forward his well-known theory of athrepsia, which may be stated briefly as follows: A tumor in order to grow continuously in an animal requires certain specific substances which permit of this growth, the nature of these substances being entirely unknown; if they are not present the tumor does not grow; when they are exhausted the tumor undergoes spontaneous regression. Like so many of Ehrlich's theories, whether right or wrong, this has led to a very large amount of important work on the nature of the resistance to tumor growth. At present, however, it is generally held that the athrepsia theory is not the best explanation of the phenomenon of resistance but that the process depends upon the vascularization of the graft by the bloodvessels of the host. If this does not occur the tumor does not develop.

This phase of the problem has been most thoroughly examined by Russell in Bashford's laboratory, and additional work has been done by Woglom and Burgess. To these workers the immunity seems to be directed against the chemotactic influences exerted by the cancer cell upon the connective-tissues of the host. There must be present in the resistant animal, either in the circulating fluid or in the tissues, something which inhibits this chemotaxis, although all attempts to determine the presence of this active cell poison have been inconclusive. It is certain that this anti-substance is not very active, for the cancer cells continue to retain their proliferative power for seven to ten days in an immune animal. At the end of this time the cells begin to die, and the graft becomes surrounded by an inflammatory exudate which impairs the nutrition. The peripheral extension of the tumor cells ceases, central necrosis occurs, and ultimately the entire mass undergoes necrosis and absorption. Da Fano (1912) has called attention to the fact that in regressing carcinomata a large number of plasma cells and lymphocytes were found in the tissues about the growth, and he thought that the immunity was in some way correlated with the presence of these cells, a point which Murphy later used very effectively.

Heredity. In 1911 Murray, of the Imperial Cancer Research Fund, published the results of careful studies on highly inbred strains of mice, two groups of which had been selected: one in which a recent ancestor was cancerous, that is, the mother or one or both grandmothers or all three, and the other in which no cancer had occurred in either the mother or grandmothers. Comparing the offspring of these two groups, it was found that in those of cancerous ancestry 18 per cent. developed tumors in later life, whereas in those with non-cancerous ancestry only 8.06 per cent. bore tumors. Actuarial discussion of the statistics led Murray to the view that the disparity between the two groups was not due to chance, but, on the contrary, was significant, and that the increased liability to cancer was in all probability in the nature of a predisposition of one organ or tissue to undergo cancerous transformation under conditions as yet not understood. These observations have been extended by Tyzzer, Leo Loeb, and Maud Slye. The results obtained by Miss Slye and by Loeb confirm Murray's conclusions,

but the subject still needs a great deal of study. Apparently not all groups of mice can be bred so as to show cancer heredity; this is possible only with certain strains. Miss Slye thinks that even organ liability can be transmitted; that is, that by suitable breeding a susceptibility to a tumor of a given organ may be carried down to succeeding generations, but this statement needs much further confirmation, both from the author and from some independent source.

The statistical study of human cancer has as yet given us no reason to think that heredity plays any part in the occurrence of the growth.

Conditions of Metastasis. The variation observed in the metastatic spread of neoplasms has always excited a great deal of interest, two somewhat conflicting views being held: one, that the extent and relative liability to metastasis are dependent on purely mechanical factors only, the size of the cells and the vascular relationships; the other, that the soil in the various organs differs in its suitability.

Tyzzer has shown recently that massage of a tumor greatly increases the number of metastases, an observation strengthening the first theory; while careful comparison of the susceptibility of different organs by inoculation tends to show that there is little or no variation, provided the tumor cells are deposited in proper amount.

Explants or Tissue Cultures. That tissue cells may grow independently of the body has been known since 1906. This property of cells was made use of by Lambert and Hanes (1913) to show, first, that tumor cells will grow in the plasma of alien species, though no growth is obtainable in the tissues of such a host; and, secondly, that tumor cells grow just as vigorously in the blood of animals immune to the tumor as in that of those free from such inhibiting powers. This demonstrates that tumor immunity is not due to antibodies present in the circulating blood.

Chicken Sarcoma. Peyton Rous, of the Rockefeller Institute, in 1910 discovered in a Plymouth Rock hen a large tumor of the right pectoral muscle. Inoculations of this growth into other hens resulted in the obtaining of a single large secondary mass.

Further transplantations were more easy, and the tumor is now an extremely malignant sarcoma which forms metastases all over the body with the greatest rapidity and kills the inoculated animals in from fourteen to eighteen days, growing in practically all of the animals inoculated. It is a sarcoma with small spindle or fusiform cells, and is usually extremely well vascularized. It does not now form nodular masses, but gives rise to a diffuse infiltrative growth throughout the organs which it involves. Metastasis takes place through the bloodvessels. The point of especial interest about this tumor is that when the growth is ground up and passed through a Berkefeld filter No. 5, which is impermeable to the *B. prodigiosus*, the resulting fluid is capable of giving rise to a new tumor when inoculated into a susceptible fowl. The same is true when tumor tissue, after being ground and dried, is inoculated, and even also when the tissue is suspended in 50 per cent. glycerin. After heating to 50° C. for fifteen minutes, the tumor will not grow *in vitro*, but such heated material when inoculated into susceptible fowls gives rise to growths. The obvious interpretation of the phenomena just mentioned is that the tumor is transmitted by an invisible and filterable virus. No parasite can be demonstrated, however, in ultramicroscopic preparations, even though the filtrate is capable of giving rise to tumors when injected. On the other hand, it is not possible to immunize against this tumor by the injection of embryo skin or whole embryos. This is, however, not an absolute proof that it is not a tumor of the ordinary type, because immunity can not be produced against all varieties of tumors. Another curious fact is that no complement-fixation is found in the blood of chickens carrying this tumor when the tumor itself is used as an antigen. This points somewhat to the fact that there is no parasite present. We evidently have here a tumor of an entirely different type from anything known in human oncology.

Heterologous Transplants. Murphy (1914) having noticed that the growth of tumors of the mouse and rat in chicken embryos was halted at the period when development of the spleen and bone marrow began, conceived the idea of attempting heterologous transplants in adult animals in which the lymphocytic reaction of the tissues had been inhibited by preliminary treatment with the

x-ray, basing his premises also upon the work of Bashford and Da Fano and Roux, who have shown that in regressing tumors a great collection of lymphocytes and plasma cells occurs about the graft. In rats treated with the *x*-rays, he was able to grow mouse carcinoma for thirty-two days, apparently confirming many of the previous suggestions that immunity to tumors lies in the tissue rather than in the serum.

Nematodes as a Cause of Cancer. Borrel has long believed that certain parasites are related to the occurrence of cancer; and Haaland has also stated that nematode worms are frequently present in breast tumors of mice. The scientific world was greatly interested, therefore, when Fibiger reported (1914) that he was able to produce tumors of the rat stomach by feeding certain nematodes which are parasitic in the cockroach. These tumors, as a rule, do not extend beyond the walls of the stomach and involve only the portions covered with squamous epithelium, but in several cases it was thought that there were metastases in the lungs or lymph-nodes; apparently, however, no attempt was made to transplant the tumors and the observation must remain as unconfirmed. Experiments in my own laboratory with the feeding of cockroaches which were known to contain the nematode in question have not resulted in any very marked hyperplasia of the gastric mucosa, and, in fact, far greater hyperplastic growth, with invasion of the submucosa and muscularis quite corresponding to the tumors which Fibiger reports, has been produced by the continuous irritation of the mucosa of the stomach with certain chemicals. These results cast some doubt on the specific nature of the parasitic irritant, which Fibiger assumed. Some of those who have seen Fibiger's sections doubt, also, the metastatic nature of the lung growths, believing rather that they represent heterotopic epithelium from the nearby bronchi. If, however, Fibiger's tumors prove to be actual malignant growths, this will be one of the very important examples of our ability to produce at will, by chronic irritation, a tumor corresponding to the well-known *x*-ray carcinomata of which many examples have been seen in man and a few in animals, notably in some experiments of Clunet, after continuous irritation with the *x*-ray.

Theories of Neoplasia. Much of the immunological investigation in cancer has been based upon the assumption that there is some close correlation with the facts of bacterial immunity. On the contrary, however, the conditions which permit bacteria to flourish are actually just the opposite to those under which tumor cells can grow in the tissues. Bacteria are active invaders of the host tissues, either fluid or solid, and act as antigens, often growing in spite of the development of a large number of antibodies which may or may not ultimately destroy the parasites. The tumor cells, on the other hand, are not parasitic in their incipiency, but rather commensals, acting parasitically on the host only when the growth exceeds a certain volume. If the tumor cell excited an immune reaction at its inception it would be destroyed, as any aberrant body cell is, by lack of nutritional supply owing to the fact that vascularization does not occur. Epithelium placed in the peritoneal cavity of an animal excites a reaction which results in a prompt destruction. A group of tumor cells, on the other hand, excites no reaction, but is soon vascularized, and, hence, survives. Both types of cells grow with ease in the plasma of the animal whose tissues have rejected one form and cared for the other; hence, the conditions of growth are not dependent upon the body fluids, but upon the tissue cells themselves, the condition being not a positive reaction against them, but rather the occurrence of vascularization which permits the cancer cells to establish themselves. The normal cells, on the other hand, incite a reaction which leads to their destruction, and it is, therefore, impossible to produce a tumor by the injection of normal epithelium, glandular structures, or connective-tissue cells.

Treatment. A few words will suffice to sum up all that we know as regards treatment of carcinoma. No simple chemical or complex organic body seems to have any permanent influence on tumor growths. Colloidal metals, autolysates, and bacterial toxins have not the slightest curative power in carcinoma either of man or of animals. A combination of selenium and eosin, so widely vaunted by v. Wassermann, has failed to fulfil its promise. Physical agents, such as *x*-rays and radium, have some actual power, but only in the superficial or less malignant forms of tumors. That

early operative excision is still the best therapeutic procedure is shown both by animal experiments and by clinical experience.

Thus, despite the most painstaking experimental study, the garnering of thirty years' work shows a surprisingly small harvest, not at all comparable with the amount learned during the same time concerning bacterial and tissue immunity. The problem seems much more difficult owing to the many variables always to be considered in working with so highly specialized and susceptible a cell as that of mammalian cancer, and because reactions following the implantation of tumor cells into the tissues are wholly different from those following the introduction of bacteria or simpler cells, such as red blood corpuscles. In fact, the striking phenomenon is that they do not produce any of the ordinary immune reactions, perhaps because they grow only in a host of the same species, for when introduced into another species, immune bodies of a non-specific nature only, exactly comparable to those induced by normal cells, are produced.

SEVERE ANEMIA WITH REMARKABLE ELONGATED AND SICKLE-SHAPED RED BLOOD CELLS AND CHRONIC LEG ULCER[1]

By JEROME E. COOK, M.D.

AND

JEROME MEYER, M.D.

ST. LOUIS

The unusual character of the blood findings in the case here recorded is alone sufficient to justify its report. When, however, we compare these findings, as well as the clinical history, with two similar cases previously reported, one by James B. Herrick, the other by R. E. Washburn, we are forced to the conclusion that we have in these three cases a group which belongs quite apart from anything heretofore described. We desire to present the history and findings in our own case, with the abstracts of the cases of Herrick and Washburn, and to show that the three have points of resemblance so characteristic and so constant that they cannot be explained as accidental. Our thanks are due to the above-mentioned authors for the opportunity of examining blood smears of their cases and for other courtesies.

Author's Case. *Personal History.* O. B., a mulatto woman, aged twenty-one years, entered the Washington University Hospital, November 3, 1914, giving the following history: She was born in St. Louis and had never been out of its immediate vicinity. She had had most of the diseases of childhood, and suffered at intervals, ever since she could remember, with "rheumatic" pains; the joints had never been swollen. Shortly after

[1] From the Department of Internal Medicine, Washington University Medical School.

her marriage, two years ago, she developed "pus tubes," which were removed a year later. At the age of five years an ulcer broke out on her ankle, which healed in about a month, under treatment. This did not recur until two years ago when a similar condition developed which lasted three or four months and was healed with scarlet-red ointment and bichlorid packs. Ten months before entering the hospital the ulcer again appeared. It caused her no pain and has been treated in various ways.

Physical Examination. November 3, 1914. The patient was a light-colored mulatto, with evidence of some loss of weight, conjunctivæ and mucous membranes rather pale. The conjunctivæ had a greenish tint. The rest of the physical examination, with the exception of the leg condition to be described, was not significant. There was a soft systolic murmur at the apex, transmitted to the left axilla, and heard over the left precordial area, the second pulmonic was louder than the second aortic and definitely accentuated. The systolic blood-pressure varied from 105 to 125, the diastolic between 60 and 65. The lungs were clear, the spleen not palpable. On the left ankle, just above the internal malleolus, was an ulcer 3 by 2 cm., the edges slightly indurated, the whole being of a light pink color. On the outer side of the ankle there was a scar 7 cm. by 3 cm. The skin in this region was dark and shiny.

Course. The ulcer soon healed under bichlorid dressings, has remained closed since, and now presents a smooth, irregular surface, not depressed, of rather glossy and somewhat transparent texture, not white, but rather of an ivory color through which a fairly close network of capillaries can be discovered on close examination. Since her discharge from the hospital, December 3, 1914, the patient has gained in weight, feels stronger, and looks in every way improved. Our principal interest has, from the first, been centred on the blood picture. This will be taken up in detail later. Its unusual character made us feel that a full knowledge of the patient's family history possessed more than ordinary importance. We were able, by consulting several sources, to obtain fairly complete and accurate data.

Family History. Patient's father, A. W., a mulatto, aged fifty-four years has no knowledge of any blood relation except his children. The patient's mother died six years ago, aged fifty-one years, of breast cancer, twenty months after the disease was first noticed. The patient is the youngest of four children, there having been two boys and another girl. The first boy died at the age of seven years. Up to a year before his death he was well nourished and apparently well; he then grew thin and sallow, had no cough, became progressively thinner, but was only confined to bed ten days before his death. The next child, a girl, died at the age of twenty-two years of tuberculosis. She was healthy up to her fifth year, after which she became thin and sallow and suffered with pains in the extremities. The

next child, a boy, died nine years ago at the age of seventeen. He was seen by Dr. E. W. Saunders, who furnishes the following note of the family at that time: "I found the children the victims of severe anemia. One of them died and then I lost sight of the family." The father says that this boy was strong and fat up to the age of six years after which he began to get weak and very pale. None of the children except our patient had leg ulcer. The patient's mother was born in St. Louis and was never outside of the city. She was a healthy woman up to the time of her last illness. The mother's family history reveals nothing significant, with the exception that there seems to have been a large admixture of white blood. The mother's sister and her daughter are living in St. Louis. They are light-colored mulattos whose general appearance bear out the statement that they are in good health. Owing to some family enmity we have, as yet, been unable to persuade these two to submit to nearer examination nor even to permit blood smears to be taken.

During the patient's stay in the hospital numerous blood examinations were made. The most striking feature was the shape of the red cells in the fresh and stained preparations. The illustrations show the condition in general, though there are many variations in each type.

Many of the red cells, about one in three, on rough count, were elongated, oat-shaped or crescent-shaped, with the same color and structure as the normal red blood cells. Some of the crescent-shaped cells in the fresh drop would curl and bend as if they were unusually pliable. There was considerable variation in the size of the red cells and also many structures which seemed to be fragments of cells, as if some of the cells had been crushed. The rather uniform character of these fragments, however, suggests that they were not artefacts. Nucleated reds were always present and at times were quite numerous. With Romanowsky stains there was only slight polychromatophilia.

The red cells varied in number between 1,800,000 and 3,100,000, usually about 2,500,000; there was at all times a leukocytosis of mild degree; the color index averaged slightly below 1, and there was a constant eosinophilia at the expense of the polymorphonuclear cells. The following counts show the variations and are selected from a large number, made at short intervals:

CELL COUNT AND HEMOGLOBIN

Date.	Red blood cells.	White blood cells.	Hemoglobin, per cent.
November 3, 1914	2,008,000	10,560	43
November 10, 1914	2,240,000	10,320	45
January 14, 1915	2,960,000	14,200	53

DIFFERENTIAL COUNTS

Date.	No. of cells counted.	Normoblasts.	Intermediates.	Lymphocytes, per cent.	Large mononuclears, per cent.	Polymorphonuclears, per cent.	Eosinophiles, per cent.	Basophiles, per cent.
November 5, 1914	1000	21	11	17.8	10.6	58.4	12.6	0.6
November 14, 1914	200	4	1	30.5	3.0	37.5	26.0	3.0
January 10, 1915	200	8	..	23.0	8.0	55.0	12.0	2.0

Before entering the Washington University Hospital, the patient had been in the Skin and Cancer Hospital. The blood examinations, made by Miss Florence Miller, clinical pathologist, show that the condition of the blood was about the same as in our experience. During the patient's stay in this institution search was also made for blood parasites, but without result.

The eosinophilia was subject to constant variation of rather wide range, and at one time we were able to follow a rise in the count from 3 per cent. to 26 per cent. within eleven days. The intense eosinophilia awakened the suspicion that the patient harbored a parasite. The stools were very thoroughly searched for evidence of this, but without avail. Nor did repeated examinations of the blood taken at all periods of the twenty-four hours, including centrifuged preparations of the citrated blood, reveal anything which could be interpreted as parasite or ovum. The Wassermann reaction was negative and an injection of salvarsan had no effect on the blood picture or the leg ulcer.

Some of the differences in shape depend on position, as can be seen by watching a fresh preparation, but we could never see the change from oval or oat-shaped bodies to worm-like or sickle-shaped, or the reverse.

The suggestion that the abnormal shapes are artificial cannot well be proved. We could not avoid getting the same forms, no matter how carefully the preparations were made, nor could we produce similar changes in normal or anemic blood from other cases. Dr. V. E. Emmel, associate professor of anatomy, who has made ex-

tensive studies of blood development and morphology, was much interested in this feature of our case, and made many investigations into possible explanations. His results will be published later.

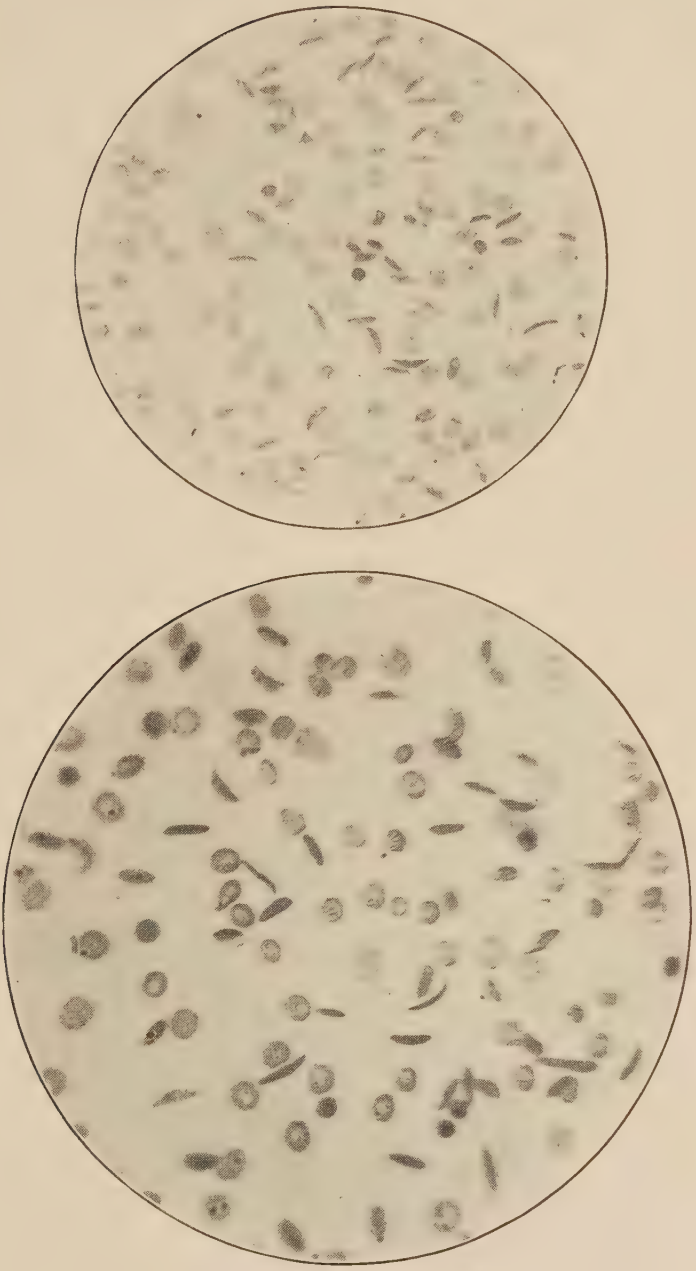
The possibility of an inherited anomaly suggested itself. The fact that the three other children of the family had suffered from severe anemia encouraged investigation in this direction. Examination of the father's blood showed 4,500,000 red cells, 11,100 white cells, and 86 per cent. hemoglobin. Differential count showed: polymorphonuclears 68 per cent., lymphocytes 20 per cent., large mononuclears 8 per cent., eosinophiles 4 per cent. The stained smear showed none of the peculiarities of the daughter's blood. Dr. V. E. Emmel, however, found some resemblance in the behavior of the blood. When preparations of the fresh blood were sealed under precautions which insured sterility and allowed to stand for several days at room temperature, the microscope revealed long, sharp projections and elongations from many of the red cells in the blood of both the father and the daughter. Dr. Emmel has not found similar appearances in the blood of any other person.

The following case was reported by Washburn:[1]

Washburn's Case. The patient had been under observation since 1907; a negress, aged twenty-five years, a native and resident of Southwest Virginia all of her life. When admitted to the University of Virginia Hospital in 1910 she complained of weakness, soreness and pain in the left side, and a sore on left leg. When a child she had pneumonia and within the last five years has had chills and fever, supposedly malaria. On admission she had shortness of breath on exertion, night sweats and swelling about the wrists and ankles. There were occasional attacks of abdominal pain and indigestion.

The patient's father, an old man, has been in bad health for many years. The mother died twenty years before. The patient had four brothers, all of whom died while small, and four sisters, three of whom died in childhood, while one died recently of some brain trouble. The patient's illness dates back five years, when she noticed some dizziness, shortness of breath on exertion and swelling about the wrists and ankles. At the same time she knocked some skin off the left shin, resulting in an ulcer. Some time later an ulcer started on her right leg, though she remembered no injury. The patient was operated on for gall-stones in 1908. In April, 1909, the

[1] Peculiar Elongated and Sickle-shaped Red-blood Corpuscles in a Case of Severe Anemia, Virginia Med. Semi-Monthly, 1911, xv, 490.



FIGS. 1 and 2.—Elongated and sickle-shaped red blood cells.

following blood examination was recorded: Red cells, 2,000,000; white cells, 11,000; hemoglobin (Sahli) 50 per cent. Differential white count was as follows: Polymorphonuclears, 63 per cent.; small mononuclears, 25 per cent.; large mononuclears, 2 per cent.; eosinophiles, 4 per cent.; mast cells, 6 per cent. The red cells showed poikilocytes in a variety of shapes, the most common being of a crescent shape. Washburn sums up his case as follows:

The case is one of severe anemia, characterized by a peculiar poikilocytosis, oligocythemia, and a color index less than one, together with nucleated red corpuscles, myelocytes and an increase in the percentage of eosinophiles. Among the suspected causes were syphilis and intestinal parasites, but both of these seem to be disproved. There is no definite history of syphilis, and the iodids, though given until the physiological effect was produced, had no apparent influence on the anemia or on the leg ulcers. No intestinal parasites capable of producing the trouble were found on examination of the stools either before or after the administration of thymol. The facts do not seem to warrant diagnosis as to the cause of the condition.

The following is abstracted from the case of James B. Herrick.[1]

Herrick's Case. The patient, a negro of twenty years, had been in the United States three months, his former residence was in the West Indies, where he was born. He was one of four children, all the others being healthy. At the age of ten years the patient had had yaws, which was common in his locality. The disease lasted about one year and was characterized by ulcers on the legs, described as pustular with scabs, the scars of which remained. For about a year previous to coming under Herrick's observation he had noticed some palpitation and shortness of breath, and for about three years had had a disinclination for exercise. On landing in New York, September, 1904, he had a sore on one ankle which healed with tincture of iodin, leaving a scar similar to those on limbs. The patient came to Herrick for treatment of a "cold." Physical examination showed a young man,well developed physically, a tinge of yellow in the sclera and pale mucous membranes. The cervical, axillary, inguinal, and epitrochlear glands were definitely enlarged. The scars to which he referred were nearly all located on the legs and thighs, perhaps twenty in all. They were rounded or oval, sometimes of irregular contour, the edges clean cut; some were like tissue paper or thin parchment to the touch and were lighter in color than the surrounding skin. They were strikingly like scars often seen as a result of syphilis. A faint systolic murmur was heard over the

[1] Arch. Int. Med., 1910, vi, 517.

base of the heart and to some extent over the apex. The blood examination on December 24, 1904 was: red cells, 2,880,000; white cells, 15,250; hemoglobin, 50 per cent. Differential count: polynuclears, 72 per cent.; small mononuclears, 15 per cent.; large mononuclears, 7 per cent.; eosinophiles, 5 per cent. Nucleated reds were common. The shape of the red cells was very irregular, but what especially attracted attention was the large number of thin elongated sickle-shaped and crescent-shaped forms. These were seen in fresh specimens no matter how the blood was spread on the slide; they were likewise always present in the fixed specimens. Under treatment the blood improved in quality, but there was still a tendency to the peculiar crescent shapes in the red cells, though this was not so noticeable as before. Nucleated reds were present. Eosinophiles made up 5 per cent. of the total white cells. On March 7, 1906, a blood count was made that showed red cells, 2,700,000; white cells, 30,500; hemoglobin, 55 per cent. Differential count: polynuclears, 58 per cent.; small mononuclears, 22 per cent.; large mononuclears, 12 per cent.; eosinophiles, 7 per cent.; myelocytes, 1 per cent. The elongated and spindle forms were numerous and there were many nucleated reds. The patient passed from observation in 1907 in about the same state of health as before.

Careful search of the literature has been made for other similar cases or for any blood picture resembling that of our case, but we have discovered no text-book or article which refers to elongated and sickle-shaped cells such as we have described. A search of this kind must of necessity be incomplete; it adds some testimony, however, to the fact of the extreme rarity of this condition. The only accounts which we have found and which, though seemingly unlike our case, may have some relation to it and are for that reason mentioned here, have been published by Bishop[1] and Dresbach.[2] The former reports a patient 70 per cent. to 80 per cent. of whose red blood cells showed "a more or less well-marked elliptical outline." Most of the elliptical cells measured 13 by 5 microns. The red blood cells numbered 5,400,000, hemoglobin 110 per cent. The sister's blood showed the same condition of the cells and her red blood cells numbered 5,000,000 with 100 per cent. hemoglobin. Four other members of the immediate family showed a normal blood picture. We are indebted to Dr. Bishop for the privilege of examining blood smears in his case. Dresbach reports a similar

[1] Elliptical Human Erythrocytes, Arch. Int. Med., 1914, xiv, 383.
[2] Science, 1904, xix.

case in a mulatto, aged twenty-two years. There were 5,000,000 red blood cells, about 90 per cent. of which were more or less oval The greatest variation showed a minimum diameter of 3.9 microns, with a maximum of 10.7 microns. A brother had normal corpuscles. In both cases the general health was good with normal red and white counts and hemoglobin and an absence of nucleated red cells.

It will be seen that there is a striking similarity in both the blood picture and the clinical history of our case with those of Washburn and Herrick. All three of the patients were of negro blood; all three suffered from peculiar, indolent, recurring leg ulcer; in all three the anemia was sufficiently severe to cause dyspnea on exertion, and in all of the cases there was a peculiar discoloration of the scleræ, which in our case and that of Washburn is described as a "greenish tinge," and which Herrick notes as "a tinge of yellow;" in no case could enlargement of the spleen be made out; responsibility for the condition could not be placed on syphilis or a parasite, although a careful examination was made in each case for such a possible etiological factor.

The uniformity of the blood abnormality is even more striking, the individual differences being of degree rather than of kind and depending no doubt to some extent upon the time at which observations were made.

The red cells in the three cases, in the numerous examinations made, varied between 1,800,000 and 3,000,000 with a striking tendency to remain around 2,500,000. In all of these cases there was a leukocytosis of more or less marked degree, and in all cases there was an eosinophilia of distinct but varying degree. A varying number of nucleated red cells were present in all cases, in no case were they rare or difficult to find. A glance at the blood slides leaves no doubt as to the identical character of the elongated and sickle-shaped red cells. The percentage of these cells was greater in our case than in the other two, but even in these it was considerable.

We wish to express our thanks to Dr. George Dock for the privilege of studying the case and for his suggestions in the preparations of our work.

DISCUSSION

Dr. W. S. Thayer: I wish to exhibit some slides showing changes similar to those in Dr. Dock's case. My patient has a grave secondary anemia, with a leukocytosis of 20,000. There is an increased resistance to hypotonic salt solution and a great increase of vitally staining cells.

THE PRESERVATION IN VITRO OF LIVING ERYTHROCYTES[1]

By PEYTON ROUS, M.D.
AND
J. R. TURNER, M.D.
NEW YORK

Methods for the preservation of living red cells outside the body are desirable for several reasons. During their elaboration some insight would almost certainly be obtained into the reasons for the rapid breaking down of corpuscles when kept *in vitro* in the ordinary manner. Kept cells might prove useful in culture media, and in serum reactions, and in transfusions even, a possibility made very real by Dr. Abel's recent work on plasmapheresis. Experiments with cells allowed to age *in vitro* and then reinjected might cast some light on the physiology of erythrocytic destruction.

For our first attempts at preservation, washed corpuscles were employed. We were able to demonstrate a factor which largely accounts for their short period of survival *in vitro*. When red cells are washed in normal salt solution, Ringer's or Locke's solution, by means of the centrifuge, they are often greatly injured, no matter how careful the technic. This injury, which is mechanical in character has its result in either immediate or delayed hemolysis. It is especially serious in the case of dog cells, less pronounced with rabbit and sheep corpuscles. Plasma will protect against it, the addition of a little to the wash fluid being sufficient. Gelatin is still better. Cells washed in Locke's solution to which one-eighth of 1 per cent. of gelatin has been added, and placed thereafter in

[1] From the Laboratories of the Rockefeller Institute for Medical Research.

ordinary Locke's solution will remain intact, dog cells for days instead of hours, and sheep and rabbit cells for several days longer than is usual. Human cells are more resistant to injury than those mentioned. They remain intact as long when washed in the ordinary way as when a protective solution is used.

The differences found in the resistance to mechanical injury of the cells of different species have led to some parallel observations on this resistance and the resistance to hypotonic salt solutions, or in other words to a comparison of the true fragility with what is often mis-called fragility. The two have little if any relation. Corpuscles notably susceptible to mechanical injury may show a striking resistance to hypotonic salt solution, and vice versa. This holds good for the cells of different individuals of one kind as well as for those of different species. A clinical investigation of the resistance of red cells to mechanical injury should prove interesting.

Though gelatin markedly protects red cells, it is not at all preservative of them. Corpuscles kept in a gelatin—Locke's solution last no longer than when in ordinary Locke's—and ordinary Locke's is, as we have found, positively injurious to cells long in contact with it. Many substances were tested for a preservative action. The sugars proved far the best, especially dextrose and saccharose. When these latter are mixed in small per cent. (2 per cent. and 5 per cent. respectively) with Locke's solution they not only prevent injury from it, but exert a remarkable action to delay hemolysis, and, as transfusion experiments show, to conserve the life of the cells. In an isotonic Locke's-dextrose mixture washed sheep cells have been kept intact for two months, and washed rabbit and human cells for several weeks. Cells thus kept go easily into suspension, pass readily through a paper filter, can be repeatedly washed without hemolysis, and will take up and give off oxygen. Sheep cells kept more than a month and used for the Wassermann reaction behave like fresh cells of the same sheep, and have the same hemolytic titre. For the preservation of human and rabbit cells no washing is necessary. They will remain intact for four weeks in citrated blood to which an isotonic, watery, saccharose solution has been added.

In order to determine whether the kept cells are still alive and

capable of functioning, many transfusions of them have been carried out in rabbits. The animals acting as recipients were bled and the corpuscle loss replaced as accurately as possible with rabbit cells kept in bulk *in vitro*, and suspended in Locke's solution for injection. In this way by repeated large bleedings and injections, much of the blood was replaced. It was found that cells which had been kept two weeks functioned perfectly. Immediately after a transfusion of such cells, the rabbits seemed normal and in the days following there was no drop in hemoglobin or red cell count, and no rise in the number of reticulated cells. The urine was free from hemoglobin and bile pigments.

The results with cells kept much longer *in vitro*, until effete, cannot yet be summarized except as regards a few points. Cells too old to function are easily disposed of by the body. In some rabbits 40 per cent. of the corpuscles were replaced with old cells. The blood examinations showed that practically all these disappeared from the circulation within the next three days. Yet the rabbits appeared normal and some of them gained in weight. There was no rise in temperature, no shadows in the blood, and no hemoglobin or bile in the urine. On *post mortem* at the height of blood destruction, the organs appeared normal save for the anemia, and in some instances for a slight increase in size of the spleen with marked phagocytosis and a pronounced iron reaction. It is evident that whatever the arrangement for the destruction of old blood, it has large factors of safety.

INTRASPINAL ADMINISTRATION OF ANTITOXIN IN TETANUS: NOTES ON A SERIES OF CASES[1]

By MATTHIAS NICOLL, Jr., M.D.
NEW YORK

(By Invitation)

As the result of a series of animal experiments conducted at the Research Laboratory of the Department of Health by Dr. William H. Park and myself[2] in order to determine the curative value of the intraspinal administration of tetanus antitoxin, and by which the superiority of this method was conclusively shown, every effort has been made during the past year to get into immediate touch with physicians and hospitals in and about the city of New York having cases of tetanus under their care, and induce them to give antitoxin as soon as possible by the following method:

1. From 3,000 to 5,000 units into the lumbar region of the spinal canal, preferably under an anesthetic, the volume of fluid injected being brought up to 10 or 15 c.c. by the addition of sterile normal saline, the exact amount being regulated according to the age of the patient and the amount of spinal fluid withdrawn.

2. Ten thousand units intravenously at the same time.

3. Repetition of the intraspinal dose in twenty-four hours.

4. A subcutaneous dose of 10,000 units three or four days later.

The well-recognized adjuvants to specific treatment—quiet, subdued light, sedatives, etc.—were, of course, understood as a necessary part of the therapeutic measures.

[1] From the Research Laboratory, Department of Public Health, New York.

[2] Experiments on the Curative Value of the Intraspinal Administration of Tetanus Antitoxin, Jour. Am. Med. Assn., July 18, 1914, p. 235.

In no case has the physician objected to giving an intraspinal injection of antitoxin when so advised. Some, however, have given it in much greater quantities and by other methods in addition to that recommended, usually before I was able to consult with them.

Reports of twenty cases have thus been collected, in all probability representing a majority recognized as tetanus during this period in and about the city of New York. I have seen about half of the patients personally, in consultation. In others, the physicians have been kept in constant touch by telephone or through a clinical assistant during the progress of the case. In four cases, the histories have been furnished by the physician on request, the treatment given being exactly that recommended by the published article referred to above. In all cases the antitoxin used was furnished by the Department of Health.

A brief abstract of the clinical histories follows:

Case I.—F. D., girl, aged ten years, seen in consultation with Drs. W. B. Anderton and A. A. Smith, fell, striking her forehead on the ground, receiving a lacerated wound three-quarters inch long over one brow. This was properly disinfected and sutured, healing promptly. Seven days later there was a facial paralysis on the side on which the wound was received. Thirty-six hours later, the jaws were firmly locked. Eight hours after this symptom was noted, the patient received 3000 units of antitoxin intraspinally and 10,000 intravenously. Several subcutaneous injections were later given. The tetanic spasms were largely confined to the muscles of the jaw and pharynx, and later, the abdominal muscles; attempts at swallowing and the slightest external irritation caused contractions of the muscles of the throat and larynx, cyanosis, general convulsions and unconsciousness. Such convulsions occurred on fifty or more occasions, together with innumerable minor spasms. Pneumonia developed later, resolution being very long delayed. After a protracted convalescence and extreme emaciation the patient made a perfect recovery.

Case II.—Thomas B., laborer, was admitted April 1, 1914, to the New York Hospital, with multiple lacerations of scalp and traumatic amputation of toes of the right foot. The wounds were immediately disinfected with iodin and irrigated with iodin solution. The following day, amputation of the toes was performed. April 10 (incubation nine days), there was slight stiffness of the jaws, which was not reported until the following morning. April 11, 1500 units of antitoxin were given in the tissues about the wound and 3500 intravenously, later on the same day, 3000 units into

the tissues about the wound and the same amount intravenously. April 12, the patient was very much worse, and was given 13,000 units intravenously, 8000 intraneurally and 7000 into the tissues about the wound. April 13, I was first consulted and the patient visited. His condition was still more unfavorable. There was marked opisthotonos. Eight thousand units of antitoxin were given into the spinal canal and 9000 intravenously. Following the intraspinal injection the temperature rose to 105; there were severe headache, convulsions and semicoma. April 14, the patient was comatose throughout the day. April 15, the patient was conscious, and there was less rigidity. April 16, there was much less rigidity; the patient swallowed fairly well for the first time. The patient continued to improve and was discharged cured, April 30.

Comment. Through a series of misunderstandings, this patient received still further intravenous injections of antitoxin following the intraspinal dosage, although an examination of his blood showed a tremendous antitoxic content. How much credit should be given the single intraspinal dose for the recovery in this case it is difficult to say. It is to be noted, however, that the first real improvement followed shortly after its administration.

Case III.—Gustav H., aged twenty-three years, carpenter, admitted to St. Vincent's Hospital, June 27, 1914, had injured the tips of his fingers in some way, June 16. A definite history could not be obtained. Three days before this the patient had a pustule on his neck, which was opened on the June 20. There was no other history of injury. June 21 (incubation five or eight days), he first noticed that his jaw was stiff; two days later, this was much more marked and had spread to the neck, back, arms and legs. On admission, there was marked opisthotonos, and the jaws were tightly locked. The slightest disturbance caused a convulsion. The patient's body rested on the heels and back of the head. The abdomen was board-like. Treatment on the first day after admission consisted of 5000 units of antitoxin intraspinally and 5000 intravenously; June 28, 5000 subcutaneously. The opisthotonos continued. July 1, 5000 units were administered intraspinally, five hours after which the patient became delirious with a rise in temperature to 105°. From July 4 to July 8, the rigidity decreased daily. July 18, the patient was discharged, cured.

Case 4.—Boy, said to have been vaccinated sixteen days previously, the vaccination wound having apparently become infected one week after vaccination, developed a slight stiffness of the jaw. Four days after the onset of this stiffness, he was admitted to the Roosevelt Hospital, where it was noted that the legs were very stiff, the arms less markedly so. There

was slight trismus. He was given, on admission, 2500 units intraspinally, 5000 units intravenously and 1500 units intramuscularly and in the tissues about the wound. The latter two injections were repeated the next day. On the third and fifth day he received intraspinal injections. Improvement in symptoms began about the third day and continued until discharge thirteen days after admission, when patient was well.

Comment. This case, though comparatively mild, was unquestionably one of tetanus. Many of the injections given could well have been dispensed with.

Case 5.—G. T., boy, aged ten years, was admitted to New York Hospital, October 9, 1914. October 2, he ran a rusty nail into the sole of the left foot. October 9 (incubation seven days), there was stiffness of jaws, and some antitoxin (dose not known) was given intramuscularly. On admission, the teeth could not be separated and there was some tension in the calf of the left leg. All reflexes increased. Eight hours after admission, 3000 units of tetanus antitoxin were given intraspinally and 1500 about the wound, which had been opened. A few hours later, 1000 were given intravenously. During the night, there were minor convulsions, accompanied by piercing screams every fifteen minutes. On October 12, there was some dysphagia, abdominal rigidity and stiffness of the neck. The teeth were separated one-half inch. Intravenous injection of 9000 units was made; there were general convulsions. October 11, there were convulsions lasting ten minutes, opisthotonos and a great deal of pain. October 12, there were convulsions for twelve minutes, stertorous breathing, cyanosis and great rigidity for half an hour following. October 13, the boy was comfortable and swallowed well. Intraspinal injection was made of 5000 units. From October 14, there was a gradual improvement. The patient was discharged cured, October 24.

Case 6.—M. B., boy, aged eight years; was admitted to Bellevue Hospital June 17, 1914. The history of injury due to a fall six days previously and the presence of an old ulcer on the right shin did not serve to establish the incubation of the disease. Five days before admission his jaw began to be stiff. This stiffness extended to other muscles day by day. On admission he was absolutely rigid from his neck to his feet. His teeth could be separated but one-fourth inch. June 18, under an anesthetic, he was given 5000 units of antitoxin intraspinally and 5000 subcutaneously. The mind was perfectly clear; the arms alone could be moved freely. There were incontinence of urine and feces. The boy was fed by gavage. June 25, he was very much improved. He bent at the waist when lifted. The mouth opened five-eights inch. June 28, he moved the legs and arms freely; the spine was no longer stiff; the mouth opened widely; he ate well.

Comment. This child was in a desperate condition at the time of giving antitoxin. On theoretical grounds we should not expect that antitoxin would be of much avail, when given at so late a period of the disease, and yet the improvement followed so soon after its administration that it would seem that antitoxin should be given the credit for it.

Case 7.—R. M., boy, was admitted to the Hospital of the Holy Family, April 15, 1914, having run a nail in the sole of his foot at some time previously not possible to determine. There was apparently locking of the jaws three days before admission, at which time the muscles of the neck and back were rigid. The wound on the sole of the foot was opened and dressed. April 16, 5000 units of antitoxin were given intraspinally, 10,000 intravenously and 3000 intramuscularly. The child's condition gradually improved, and he was discharged cured about two weeks after admission.

Case 8.—D. R., boy, aged ten years, a patient of Dr. Ramsdell, of White Plains, complained, September 14, 1914, of pain in the back and slight stiffness of the jaw and of left arm. This child was vaccinated August 17. August 31, the vaccination wound, not having been dressed for nine days, was in an unfavorable condition, there being considerable pus at the site of vaccination and swelling of the arm. A shield was later applied, on the mother's initiative. There was a further history of injury to the wound on several occasions. The incubation of the disease could not, therefore, be determined. The symptoms of tetanus increased until September 18, when the patient was given an intraspinal injection of 5000 units of antitoxin and 45,000 units (through a misunderstanding) intravenously. Following this, there was a marked exaggeration of all the symptoms; a rise of temperature and opisthotonos, lasting about forty-eight hours. The patient gradually improved and was discharged cured in two weeks.

Case 9.—Boy, aged six years, a patient of Dr. Joseph Wheelwright, gave a history of trauma nine days before the locking of the jaws. Forty-eight hours later an intraspinal injection of 5000 units and intravenous injection of 10,000 units of antitoxin were given. Subsequently this was repeated. The case was a very severe one with many convulsions, and the patient recovered fully in the fourth week.

Case 10.—A., male, at St. Vincent's Hospital, following a traumatic amputation of finger fourteen days previously, developed severe spasms of the abdominal muscles; later his jaw became locked and the rigidity was general; there were a number of convulsions. Thirty-six hours after the development of symptoms, 5000 units of antitoxin were given intraspinally and 10,000 intravenously. There was marked anaphylaxis immediately following the injection with urticaria covering the entire body and

suggestion of edema of the glottis and lungs. This passed away shortly after the administration of a large dose of epinephrin. The intraspinal dose was repeated forty-eight hours afterward, as the patient had grown worse and had had a number of convulsions. The serum reaction following this was not so severe as in the first instance. Improvement in symptoms began to show in two or three days, the patient making a perfect recovery from his tetanus, but developed mental symptoms consisting of intermittent attacks of acute mania and delusions of persecution. After a number of weeks this completely disappeared and his condition was normal.

Case 11.—T. D., woman, aged thirty years, was seen by Drs. William H. Ross and H. E. Chauvin, of Brentwood, N. Y., September 30, 1914. She had given birth to a child two weeks previously in very dirty surroundings. The symptoms of tetanus were very marked and many convulsions continued for five days. Two days after the onset of symptoms, 10,000 units of antitoxin were given intraspinally and 5000 intravenously; the later dose was repeated three times in three successive days. The patient was discharged cured except for a slight trismus which lasted for three days longer, October 11.

Case 12.—R. W., boy, aged eleven years, was seen by the physicians mentioned above September 6, 1914. There was a wound over one patella, received eleven days previously. Five thousand units of antitoxin were given intraspinally and 5000 intravenously on the day following the development of symptoms. The intravenous dose was repeated. Eight convulsions occurred during the first three days, the temperature running high during this time. The patient was discharged cured eight days after admission.

Case 13.—W. M., man, aged twenty years, seen by the same physicians January 3, 1915, had received a punctured wound of the instep three weeks previously. There was complete trismus and stiffness of the whole body. Ten thousand units of antitoxin were given intraspinally and 5000 intravenously the day after the symptoms were noted. The intravenous injection was repeated the next day. The patient was discharged cured in two weeks.

Case 14.—M. G., woman, aged twenty-two years, gave no history of traumatism. Four days before admission to the Lebanon Hospital there was slight rigidity of the neck and difficulty in opening the mouth. The next day the jaws were completely locked. On the day before admission she had general convulsions. On the day following admission, five days after the onset of symptoms, she was given 5000 units of antitoxin intravenously and 750 units intraspinally. On the second and third days she was given 5000 units intraspinally under an anesthetic. The patient also received injections of magnesium sulphate (25 per cent.) subcutaneously and intramuscularly three times a day in doses of 30 c.c. for seventeen days, without apparent relaxing effect. The course of the disease was rather

protracted with many convulsions. The patient was discharged cured seven weeks after admission.

Case 15.—L. M., male, aged eighteen years, was admitted to St. Peter's Hospital, March 27, 1915, with a crushed and lacerated wound of the great toe. The wound was immediately disinfected and properly dressed. March 30, the tip of the toe sloughed off. April 6, the patient had a severe chill and complained of sore throat. There was noted a slight stiffness of the jaw. In the afternoon there were marked stiffness of the back, and occasional slight convulsions when the patient was disturbed. Twenty thousand units of tetanus antitoxin were given intraspinally four hours after the occurrence of the chill. On April 7, the symptoms increased in severity, convulsions occurring on the slightest irritation. There were marked opisthotonos and rigidity. Ten thousand units of antitoxin were given intraspinally under an anesthetic. On April 8 the patient's condition was about the same. Ten thousand units of antitoxin were given intravenously. After the tenth day, the convulsions stopped; the rigidity continued some time longer. April 22, the patient was up and about with slight rigidity. He was discharged cured a few days later.

Case 16.—M. S., man, aged twenty-four years, admitted to Bellevue Hospital February 4, 1915, with very indefinite history, was said to have run a splinter into his foot three weeks previously. Two days before admission he complained of great pain in his back and neck, which was stiff; later he could not open his mouth. On examination the day after admission, it was found that his jaw was markedly locked, the abdominal muscles of board-like rigidity, and the back slightly arched. He was given 5000 units of antitoxin in the spinal canal and 10,000 in the vein. The intraspinal dose was repeated two days later. The symptoms increased in severity for a day or two, frequent tonic spasms causing the patient to cry out with pain. After a few days all symptoms began to ameliorate, and he was completely well in about two weeks.

FATAL CASES

Case 17.—O. R., man, aged thirty-four years, was admitted to Bellevue Hospital, November 5, 1914, for a lacerated wound of the sole of the foot, which, although treated, became infected with a foul-smelling, purulent discharge. November 12, seven days later, the patient complained of difficulty in swallowing, and the jaws were stiff. He received 1500 units of antitoxin intramuscularly, and twenty-four hours later, 10,000 units intraspinally and 10,000 intravenously. November 12, the temperature was lower, the jaws less stiff and the general condition improved, when the patient became markedly cyanotic, went into a condition of status epilepticus and died in twenty minutes. No necropsy was held. The exact

reason for the sudden death of this patient, when the course of the disease had apparently been arrested, is by no means easy of explanation.

Case 18.—J. O., man, aged thirty-two years, admitted to St. Peter's Hospital, November 13, 1914, had stepped on a rusty nail, November 1. Seven days later, his jaw became stiff. This stiffness increased until the time of admission, when his teeth could hardly be separated. The muscles of the back and neck were stiff. November 13, five days after the onset of symptoms, he received 6000 units of antitoxin intraspinally and 5000 intramuscularly, the next day, 5000 intramuscularly and 5000 intravenously, and on the following day, 5000 units intravenously and 7000 intramuscularly. The patient had tonic and clonic convulsions in great numbers throughout the course of his illness. On the day before his death, the tonicity of the neck, jaws, and abdomen had greatly diminished. He died following a convulsion, November 17. The short incubation in this case and long delay before beginning treatment are sufficient reasons for the failure of the antitoxin to save this patient's life.

Case 19.—E. C., boy, aged thirteen years, admitted to Bellevue Hospital, June 30, 1914, fourteen days previously had fallen and cut his head. Eleven days later he had abdominal pains and vomiting, which were regarded as due to appendicitis. On admission to the hospital he had marked opisthotonos, locked jaws and inability to swallow. A convulsion occurred on the slightest disturbance. He received 10,000 units of antitoxin intraspinally and 10,000 units intramuscularly. The patient's condition grew worse from the time of his admission and he died within twenty-four hours. The disease had evidently progressed too far to be influenced by antitoxin.

Case 20.—W. R., physician, aged fifty-three years, was admitted to the French Hospital for herniotomy, which was performed, April 25. May 3, the patient complained that his neck felt stiff; May 4, this symptom was more pronounced and there was some rigidity of the jaw. Toward evening he could not open his mouth fully. He was given about 9000 units of antitoxin intramuscularly. May 5, he had a general convulsion and became quite cyanotic; this was repeated twice, convulsions lasting about ten minutes. Five thousand units of antitoxin were given intraspinally and 15,000 intravenously. May 6, the patient had four convulsions, one lasting fifteen minutes. Five thousand units of antitoxin were given intraspinally. May 7, there were no further convulsions. The patient was able to take fluids by mouth, and there was much less rigidity. At 8 o'clock in the evening he had a sudden attack of pulmonary edema and rise of temperature. Later there were signs of acute cardiac dilatation. He died on the morning of May 8. This patient was very stout, and had chronic bronchitis and recurring attacks of asthma.

In judging the effect of antitoxin given intraspinally in this series of cases, it must be remembered that the patients were not selected, but that every case of tetanus reported was given the benefit of the treatment regardless of the clinical condition. The series therefore may be said to be fairly representative of the type of the disease occurring in and about the city of New York. A few of these patients would undoubtedly have recovered if the intraspinal injection of antitoxin had not been given or, indeed, without any treatment other than symptomatic. The results obtained, however, in the saving of life are so much more favorable than those in previous years, when large doses of antitoxin were recommended to be given by the intravenous and subcutaneous methods, that there can be no reasonable doubt that the low death-rate, 20 per cent., here obtained was largely due to intraspinal dosage.

I wish to express my thanks to the following physicians, in addition to those mentioned above, for allowing me the privilege of seeing the patients in their hospital service, furnishing me with clinical histories and permitting publication of extracts from them: Drs. Charles L. Gibson, George Stewart, John S. Thatcher, La Fetra, Joseph B. Bissell, M. S. Kakels, Charles Nammack and Frank Overton of the State Department of Health.

OBSERVATIONS ON PLASMAPHERESIS*

By B. B. TURNER, E. K. MARSHALL, Jr.
AND
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(From the Pharmacological Laboratory of the Johns Hopkins University[1])

In a previous paper[2] Abel, Rowntree and Turner described a method of removal of plasma from the living animal by repeated bleedings, with return of the corpuscles after they had been washed and separated in a centrifugal machine. This procedure, for which the name plasmapheresis was suggested, was found to allow of the removal of very large quantities of plasma without apparent harm to the animal, and the possibility was discussed of its application as a therapeutic measure in various cases, especially such as those in which venesection was already known to have certain beneficial effects and in which the production of anemia was to be avoided. At the same time the necessity of further study and of guarding against possible dangers was clearly indicated.

The present investigation was undertaken with the twofold object of supplying certain experimental data not contained in the previous paper, *i. e.*, chemical analyses, temperatures, determinations of blood-pressure and a continuous serise of corpuscle counts, and of acquiring further experience of the permissible limits of bleeding by this method as to rate and total amount removed.

The character of the changes in the chemical composition of the blood produced by plasmapheresis is clearly shown in the following tables, in which the general qualitative agreement of the results is obvious.

* Presented by Dr. John J. Abel

TABLE I.—PLASMAPHERESIS FOR ONE DAY, ON THREE DOGS

Date.	December 21.		January 11.		January 18.	
Weight of dog	15.1 kg.		11.9 kg.		7.1 kg.	
Blood volume estimated at 7.5 per cent.	1132 c.c.		892 c.c.		532 c.c.	
Total volume bled and per cent total blood*	1185 c.c. = 105%		1150 c.c. = 129%		410 c.c. = 77%	
Number of bleedings	3		3		5	
Results of analyses: Percentages.	Before Plasmapheresis.	After Plasmapheresis.	Before Plasmapheresis.	After Plasmapheresis.	Before Plasmapheresis.	After Plasmapheresis.
Total protein of blood	22.27	25.23	25.15	25.32	17.34	17.19
Protein of plasma	6.62	3.63	6.59	3.17	6.28	3.68
Difference of above*	15.65	21.0	18.56	22.15	11.06	13.51
Blood counts, millions	9.0	11.7	11.8	12.9	6.6	7.5
Total non-protein N	0.037	0.039	0.029	0.036	0.045	0.055
Urea nitrogen	0.016	0.019	0.011	0.017	0.016	0.023
Non-urea nitrogen	0.021	0.02	0.018	0.021	0.029	0.032
Amino nitrogen	0.0041				0.0048	0.0048

* Blood taken for analysis not included unless made up by equal amount of washed corpuscles from other dogs.

TABLE II.—CONTINUED PLASMAPHERESIS ON A DOG FOR FIVE SUCCESSIVE DAYS, JANUARY 22 TO 26 INCLUSIVE

Weight of dog, 8.5 kg. Estimated blood volume (7.5 per cent.) = 640 c.c.
Total blood removed in five days, 3335 c.c. = 521 per cent.
Analytical results in percentage of total blood.
A, before plasmaphæresis; B, after plasmaphæresis.

Date.	A, Jan. 22	B, Jan. 22	B, Jan. 22	B, Jan. 26	Feb. 19
Total protein of blood	19.28	19.31	16.81	15.83	11.78
Plasma protein	6.38	3.44	2.23	2.92	5.75
Difference of above	12.90	15.87	14.58	12.91	6.03
Blood count, millions	8.50	8.50	7.50	6.50	3.50
Total non-protein nitrogen	0.035	0.040	0.037	0.042	0.030
Urea nitrogen	0.013	0.019	0.014	0.021	0.012
Amino nitrogen	0.0047	0.0056	0.0033	0.0059	0.0038

In all cases the protein content of the plasma circulating in the vascular system is lowered by the operation, as might be expected. The extent of the reduction is, however, not as great as if an inanimate system of the same volume were submitted to the same procedure.

In contrast to the above, the other factors determined show a consistent rise. This is not surprising in the case of the corpuscle protein, which varies roughly proportionately with the blood count, the rise of which is discussed later. That the non-protein nitrogen, and those of its fractional constituents which have been determined, *i. e.*, urea and amino-acids, should also rise as a con-

sequence of plasmapheresis was not anticipated. Two possible causes suggest themselves for this increase in the urea of the blood, either (1) a reduction of excretion of urea by the kidneys, or (2) an increase in nitrogenous metabolism. As complete studies, on nitrogenous metabolism in connection with plasmapheresis have not yet been carried out, it is impossible at present to decide between these hypotheses.

Determinations of the changes in number of the red and white corpuscles, the percentage hemoglobin content of the blood, and of the temperature, gave interesting results. During one day's work it was consistently noticed that the red count and hemoglobin content of the blood rose, that the white count fell, and that the temperature rose from 1° to 2°. During the night the red count fell, together with the temperature, while the white count increased very markedly.

The rise of temperature with the following increase in the white cells did not in these experiments appear to be due to infection. The paradoxical increase in number of red cells when blood is drawn may possibly be explained by an attempt on the part of the body to regain a constant oxygen content of the blood. This matter is more fully taken up in a paper by one of the present authors which is published in the same volume as this investigation.[3]

Blood-pressures were systematically taken during the course of these experiments by a simple apparatus devised by one of us (B. B. T.) which could be easily slipped into the femoral artery and by means of which readings could be taken over periods of several days. It was found that during the day the pressure gradually fell, rising again by the next morning to nearly normal. That any pressure lower than 80 mm. is a danger signal, though 50 mm. may often be reached without collapse.

In the first paper on plasmapheresis by Abel, Rowntree and Turner it was shown that large quantities of blood, amounting in one case to more than twice the estimated volume of circulating blood could be withdrawn by this method in one day by repeated bleedings without apparent injury, and as much as three volumes in the course of three days, and the hope was expressed that these limits could be further extended.

TABLE III.—INFLUENCE OF PLASMAPHERESIS ON BLOOD COUNTS AND TEMPERATURE

Experiment No.	Date.	Volume bled.	Reds, millions.			Hemoglobin.		Whites, thousands.			Temperature.		Remarks.
			Before.	After.	Rise.	Before.	After.	Before.	After.	Change.	Before.	After.	
		per cent.				per cent.	per cent.						
1	Dec. 12	60	8.2	8.6	0.4	...	...	14	13	− 1	37.0	40.5	Overbled.
	Dec. 15	141	8.4	11.2	2.8	98	120	63	70	+ 7	39.5	..	Died.
2	Dec. 21	110	9.0	11.7	2.7	125	142	..	..	..	38.3	..	Overbled.
	Dec. 22	75	9.2	10.5	1.3	108	..	..	..	..	40.6	..	Died.
3	Jan. 11	128	11.4	12.9	1.5	..	140	..	..	..	..	..	Ether; preliminary operation 2 hours before count.
4	Jan. 15	84	9.4	10.5	1.1	..	..	..	..	..	..	..	Ether; kymograph; collapse; died.
5	Jan. 18	76	6.7	7.5	0.8	..	..	..	..	..	..	..	Ether; kymograph; collapse; died.
6	Jan. 22	113	8.5	9.7	1.2	..	..	..	..	..	38.5	39.0	See table IV for intermediate counts and table V for after period.
	Jan. 23	78	7.2	6.7	−0.5	..	..	..	..	..	38.0	38.7	
	Jan. 24	130	6.0	7.6	1.6	..	..	..	..	..	..	38.0	
	Jan. 25	115	5.2	7.0	1.8	..	..	..	..	..	38.5	38.5	
	Jan. 26	85	5.3	8.0	2.7	..	..	..	..	..	38.0	38.5	
7	Mar. 9	103	8.5	11.8	3.3	115	140	16	13	− 3	38.0	40.0	
	Mar. 10	105	10.0	11.0	1.0	130	150	50	33	−17	39.0	40.0	
	Mar. 11	34	8.5	..	..	128	..	31	..	..	38.7		
	Mar. 12	158	10.0	..	..	123	..	25	..	..	38.5	..	Died of overbleeding.
8	Mar. 15	70	10.3	10.6	0.3	120	145	20	11	− 9	38.3	39.5	
	Mar. 16	80	10.2	11.3	1.1	127	130	77	27	−50	38.5	40.0	
	Mar. 17	81	9.5	..	..	120	..	54	..	..	38.0	..	Collapse; saved.
9	Mar. 18	125	9.2	..	..	110	120	12	..	..	38.7	39.5	Gelatin transfusion died in night.
14	Mar. 22	88	8.0	10.7	2.7	115	125	12	6	− 6	38.0	39.0	
	Mar. 23	21	10.1	..	..	130	..	23	..	..	38.7	..	Collapse; internal hemorrhage; died.
15	Mar. 23	59	6.8	..	..	97	..	..	..	..	38.5	40.0	
	Mar. 24	58	7.1	..	..	82							
	Mar. 25	59	6.7	..	..	..	..	..	..	..	39.0	40.0	
	Mar. 26	53	5.8	6.5	0.7	80	65	35	47	12	38.5		

The maximum total amount which can be withdrawn by plasmapheresis has been raised in the present investigation to over five volumes, removed in the course of five days. The animal survived more than three weeks, and then only succumbed, as we believe, to accidental infection. In this respect the earlier expectations have been realized, and still further progress may be possible with care, in certain cases.

Although much time has been devoted to determining by a series of experiments on extensive and prolonged plasmapheresis the safe limits of the process, an unfortunate occurrence has somewhat vitiated this work. The imported hirudin which was used interchangeably with the extract of leech heads which we prepared ourselves, was found, contrary to the repeated testimony of earlier workers to be highly toxic, as is shown in a paper by E. K. Marshall, Jr., appearing in the same volume as this work.[4] This factor, which was not ascertained till the end of the present investigation is certainly accountable for many deaths observed, and probably lowered the resistance of other dogs which succumbed eventually to overbleeding. As no record was kept as to which kind of hirudin was used in each experiment, it is impossible at this time to eliminate all the experiments in which the toxic hirudin was used. On the other hand the large amounts of blood which have been withdrawn in many cases with comparative impunity, even though a certain amount of the hirudin used is known to have been of the toxic kind, indicate the probability of still greater success where good hirudin alone is used.

REFERENCES

1. See Jour. Pharm. and Exper. Ther., July, 1915, vii, Nos. 1 and 2, 129, for full details of this investigation.
2. Jour. Pharm. and Exper. Ther., 1914, v, 625.
3. Jour. Pharm. and Exper. Ther., July, 1915, vii, Nos. 1 and 2, 169.
4. Jour. Pharm. and Exper. Ther., July, 1915, vii, Nos. 1 and 2, 157.

A SIMPLE METHOD FOR DETERMINING VARIATIONS IN THE HYDROGEN-ION CONCENTRATION OF THE BLOOD

By L. G. ROWNTREE, W. McKIM MARRIOTT
AND
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PRINCIPLE OF THE METHOD. By means of dialysis against 0.8 per cent. salt solution the proteins and coloring matter of the blood are excluded from the dialysate, which contains salts and is well adapted to the use of an indicator. Phenolsulphonephthalein is added to the dialysate and the solution so obtained is compared with a series of standard colors of known hydrogen-ion concentration until the corresponding color is found.

MATERIALS REQUIRED. 1. *Standard Colors.* These are prepared as follows:

(*a*) $\frac{1}{15}$ mol. acid or primary potassium phosphate; 9.078 grams of the pure recrystallized salt (KH_2PO_4) are dissolved in freshly distilled water and made up to 1 liter.

(*b*) $\frac{1}{15}$ mol. alkaline or secondary sodium phosphate; the pure recrystallized salt ($Nc_2HPO_4.12H_2O$) is exposed to the air for from ten days to two weeks, protected from dust. 11.876 grams are then dissolved in freshly distilled water and made up to 1 liter.

If sufficiently pure the solutions will give a deep, rose-red color with phenolsulphonephthalein. The solutions are mixed in the proportions indicated below to obtain the desired p H:[1]

[1] To avoid writing large figures it is customary to use the logarithmic notation and to express, for example, $\frac{1}{10000000}$ N as 10^{-7} N, or, more conveniently, as suggested by Sörenson, to drop the 10 and minus sign and say p H 7. The higher the exponent, the more alkaline, or what is saying the same thing, the less acid is the solution.

p H	6.4	6.6	6.8	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	8.0	8.2	8.4
Primary potassium phosphate, c.c.	73.0	63.0	51.0	37.0	32.0	27.0	23.0	19.0	15.8	13.2	11.0	8.8	5.6	3.2	2.0
Secondary sodium phosphate, c.c.	27.0	37.0	49.0	63.0	68.0	73.0	77.0	81.0	84.2	86.8	89.0	91.2	94.4	96.8	98.0

Three c.c. of each of the mixed solutions thus obtained are placed in suitable test tubes (100 x 10 mm., inside measurement). Five drops, 0.3 c.c., of an aqueous 0.01 per cent. solution of phenol-sulphonephthalein are added to each tube. The tops are sealed off. The series of colors, representing different concentrations of hydrogen-ions, constitutes the standards for comparison in carrying out the determination.

2. *Collodion Sacs.* One ounce of celloidin (Anthony's negative cotton) is dissolved in 500 c.c. of a mixture of equal quantities of ether and ethyl alcohol. The solution should stand for at least three or four days, after which the clear supernatant solution is ready for use. A small test-tube (120 x 9 mm., inside measurement) is filled with this mixture, inverted, and half the contents poured out. The tube is then righted and the collodion allowed to fill the lower half again. A second time it is inverted and rotated on its vertical axis, the collodion being drained off. The tube is then clamped in the inverted position and allowed to stand for ten minutes. It is filled five or six times with cold water, a knife-blade is run around the upper rim, and a few centimeters of water are run down between the sac and the glass of the tube. By gentle pulling the tube is extracted, after which it is preserved by complete immersion in water.

3. *Salt Solution.* An 0.8 per cent. solution of sodium chloride is employed. This must be free from alkali and from acids other than carbonic. It is best kept in a Jena glass flask, protected from acids in the air by means of a soda lime tube.

TECHNIQUE OF THE METHOD. The determination my be carried out on serum or whole blood (oxalated).[1] The work must be done in a room free from fumes of acids or ammonia. From 1 to 3 c.c. of clear serum or of blood is run, by means of a blunt-pointed pipet, into a dialyzing sac which has been washed both inside and outside with salt solution and which has been tested for leaks by filling with salt solution. The sac is lowered into a small test-tube (100 x 10 mm., inside measurement) containing 3 c.c. of the salt solutions until the fluid on the outside of the sac is as high as that

[1] The blood is collected in tubes containing a little dry powdered sodium oxalate (free from carbonate).

on the inside. It is allowed to remain five minutes. The sac is removed and five drops of the indicator are thoroughly mixed with the dialysate. The tube is then compared with the series of standards until the corresponding color is found. This indicates the hydrogen-ion concentration present in the dialysate, and for practical purposes may be regarded as the hydrogen-ion concentration of the blood or serum on which the determination has been carried out.

Results Obtained with the Method. Oxalated blood from normal individuals gives a dialysate with a hydrogen-ion concentration varying from 7.4 to 7.6, while that of serum ranges from 7.6 to 7.8. In a small series of cases of clinical acidosis, in which the test has been carried out the serums have varied from 7.55 to 7.05 and the oxalated blood from 7.3 to 7.05.

This method is being utilized in the study of the buffer value of the blood in health and in disease by adding to blood or serum varying amounts of N/50 acid and alkali and determining the hydrogen-ion concentration of the dialysate.

THE TREATMENT OF ACUTE LOBAR PNEUMONIA BY SPECIFIC METHODS

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The scientific endeavors to discover a specific therapy for acute lobar pneumonia have all been made within the life-time of this society. The specific agent in this disease had only been obtained in pure culture by Fränkel two years before its first meeting. High hopes must then have been held that within a short time the etiologic agent might be destroyed within the body.

At the request of the President the present communication is of the nature of a stock-taking, an endeavor to answer the question whether in reality any progress has been made toward the solution of the problem of specific cure, and if so, how much, and in what direction.

In 1886, the year of the first meeting of this society, the fundamental and important observation was made by Fränkel that animals which had received a non-lethal dose of pneumococci were later resistant to a dose of pneumococci which, in an animal not previously injected, would prove fatal. In 1891 G. and F. Klemperer, Foa and Carbone, Emmerich and Fowitzky demonstrated that the blood serum of such an immune animal, when injected into a second animal, was protective against lethal doses of pneumococci or, when injected after the infection had occurred, might even be curative. All the work that has been done concerning the treatment of pneumonia by the employment of the reaction of immunity has consisted in a study and elaboration of these fundamental observations, made twenty-five years ago.

In 1912 Morgenroth demonstrated that a chemical compound,

ethyl hydrocuprein, had a specific affinity for pneumococci, destroying them *in vitro* and also *in vivo*. This discovery marks the first demonstration of a drug specifically killing *bacteria* in the animal body without destroying the host, and undoubtedly marks an epoch in the treatment of bacterial infection. These facts which I have mentioned are the only ones well established by animal experimentation from which, at the present time, attempts directed toward the practical application of specific therapy can proceed.

In both of these directions cure of pneumococcus infection is theoretically possible. Have the attempts along either of these lines been, to any degree, successful, and if not, why?

First, as to specific immunization, either actively by vaccines or passively by means of immune serum. The immunological response of the body to foreign substances introduced parenterally, either bacteria or foreign proteins, is so specific as to be astounding. To hope to make use of such reactions therapeutically it is absolutely essential that we be sure of the etiological agent in the cases treated. The studies made concerning the association of bacteria with pneumonia and the attempts to reproduce the disease experimentally indicate conclusively that pneumococci do not constitute the only cause of acute lobar pneumonia; other bacteria may also be responsible. Moreover, the studies of Neufeld and Haendel have brought definite evidence that all pneumococci are not identical as regards immunological reactions. Further studies have shown that the pneumococci isolated from patients with pneumonia may be divided into distinct groups as regards their immunological reactions, groups with characteristics as distinct and different as are the immunological characters of entirely different species of bacteria. At present three such large groups have been well established, and in the fourth group are included the organisms having no such common characters.

These facts indicate that, so far as specific therapy is concerned, the disease pneumonia can no longer be considered merely as a pathological entity, but must be considered from the point of view of etiology.

In the practical application of specific therapeutic methods in the past, however, no attempt has been made to differentiate even

the cases due to Friedländer bacilli or to streptococci from those due to pneumococcus infection. This lack of etiological differentiation renders it difficult to estimate the results of any efforts made in the past to employ specific therapeutic methods.

Active Immunity. The efforts to obtain therapeutic results in pneumonia by means of the methods employed in *active immunization* have occurred almost entirely since the introduction of so-called vaccine therapy into medicine by Sir Almroth Wright. It is impossible here to enter into a discussion of the efficacy of this form of therapy in chronic diseases. In an acute infection like pneumonia, experimental evidence which would seem to justify their use is lacking.

The evidence so far accumulated indicates that recovery in pneumonia is associated with an immunity reaction; the patient recovers because he becomes immune. At the time of crisis and during recovery the blood and tissue fluids of patients acquire properties identical with those appearing in the fluids of animals at the time they begin to exhibit active immunity. Such properties are power of agglutination, bacteriotropic or opsonic power, and the power of protecting animals from artificial infection. From analogy, therefore, it seems probable that natural recovery in pneumonia is associated with the development of active immunity and is probably dependent upon it. The only possible reason at present to justify the use of vaccines in this disease is that such vaccines might produce an earlier, accelerated development of active immunity, or a more effective one. Studies which we have carried out in rabbits, using various kinds of pneumococcus antigens, living and dead bacteria, have in no case enabled us to demonstrate the occurrence of active immunity within five days, and usually not within six or seven days, after the injections are made. This is in agreement with the observations of many others, using all sorts of bacteria and foreign proteins as antigens. Whether the immunity produced in the organism naturally infected with pneumococci may be rendered more effective by the administration of vaccines, or whether the production of immunity in an animal or patient, otherwise unable to react, may be stimulated in this way, must remain at present unsettled. At present there is no evidence

based on animal experimentation to suggest it, and a review of the literature does not convince me that the administration of pneumococcus vaccines has been proved to be of any therapeutic use. It must be stated that no extensive employment of vaccines has apparently yet been made with conscious consideration of all the known facts of pneumococcus immunity. The question of differences of types of pneumococci has not been considered in the efforts that have been made. Our own experience indicates that it is as hopeless to try to produce active immunity to pneumococci of type I by the injection of antigens prepared from pneumococci of type II as it would be to employ for this purpose colon or proteus bacilli.

The evidence, however, is growing that in active immunity to pneumococcus infection the body acquires certain properties besides those present or exhibited in the blood. This non-humoral immunity is undoubtedly of very great importance in recovery. Methods for stimulating the body to acquire it would undoubtedly be of very great importance.

Passive Immunity. A long series of attempts have been made by Pane, Washburn, Römer and others to employ the serum of immunized animals in the treatment of pneumonia in man. Has any real progress been made? Whereas there seems little or no experimental justification for the attempt to produce active immunity, there seems very convincing evidence, based on animal experimentation, why the methods of passive immunization should be effective.

While active immunity of low grades may be present in animals without the appearance of demonstrable immune properties of the blood, we have never seen the appearance of the latter without true immunity being present. Even in patients, as I have said, recovery is accompanied by the development of these immune properties of the serum.

Whether or not progress has been made in the effort to apply this principle practically, studies of the past years have shown certain reasons why the attempts previously made were bound to be failures. (1) There was no knowledge of different types of pneumococci and no effort was made to administer in a given case an

immune serum effective against the organism causing the infection; (2) the sera employed were not of sufficient immunizing power to be effective; (3) they were not employed in sufficient doses and over a sufficiently long time to have any possible effect. What has been the progress toward overcoming these defects in the employment of immune serum?

First, it is now possible to determine quickly, in each case, the type of pneumococcus causing the infection, or, if not a pneumococcus, the variety of bacteria concerned. The following chart shows the relative frequency of pneumonia due to the different types of pneumococci and different kinds of bacteria in our experience. It also shows the mortality in the cases not specifically treated.

Etiological agent.	No. of cases.	Percentage incidence.	Mortality in cases not treated with serum. Per cent.
Pneumococcus type I	78	33	25.0
" " II	75	32	29.0
" " III	22	9	45.0
" " IV	48	20	12.5

Other bacteria:

Influenza bacillus	5	
Streptococcus	3	
Streptococcus mucosus	1	
Staphylococcus	2	
Bacillus Friedländer	2	
Streptococcus, staphylococcus, and influenza bacillus	1	14
Total		237

Dr. Russell Richardson of the Pennsylvania Hospital has also determined the type of pneumococci concerned in a considerable number of cases, and has allowed me to refer to his figures.

Etiological agent.	No. of cases.	Percentage incidence.	Mortality in cases not treated with serum. Per cent.
Pneumococcus type I	60	31	30
" " II	39	20	25
" " III	13	6	50
" " IV	83	43	12
Total	195		

The figures indicating percentage of incidence in the two series are not exactly comparable, since Dr. Richardson has not included

in his list the cases due to organisms other than pneumococcus. It is evident, however, that the figures in the two series are quite similar and indicate that the majority of cases are due to types I and II, and that these cases show a mortality of from 25 to 30 per cent. Further, the cases due to type III are relatively infrequent, but the mortality among them is very high. Lastly, the frequency of occurrence of cases due to pneumococci of type IV probably differs in different places and at different times. The mortality in this type of infection is relatively small.

Experimental studies have shown that the demonstration of immune bodies in the serum of animals immunized against organisms of type III, *Pneumococcus mucosus*, is very difficult, and that probably no effective use of such a serum is possible. The fact that each race of pneumococcus of type IV is immunologically distinct precludes the use of immune serum in this type of infection.

The question of treatment of pneumonia by means of specific serum therefore at present resolves itself into the treatment of cases due to organisms of type I and type II. Since, however, these cases comprise 65 per cent. of all cases of pneumonia, and 70 per cent. of the deaths are due to organisms of these types, the possibility of influencing cases of these types, or of either one of them, is of considerable importance.

It is now possible to produce sera of much higher power than those formerly obtained. The method introduced by Neufeld, consisting in the injection of washed living virulent cultures directly into the circulation, marked a distinct advance in the production of antipneumococcus serum. Lately experiments on rabbits have indicated that by the injection of living cultures combined with immune serum it may be possible to produce sera of still greater efficacy. Studies have shown that it is possible to produce serum of considerably greater effectiveness against organisms of type I than against those of type II, the latter organisms being immunologically more closely related to Pneumococcus mucosus. Lastly, observations in the use of anticholera serum have demonstrated that it is possible to introduce large amounts of immune horse serum directly into the veins of human patients without harm. It is therefore now possible to carry on very intensive treatment of

patients with antipneumococcus serum and to overcome all those objections to the use of immune serum previously stated.

Employing the method I have outlined, a number of patients in the Hospital of the Rockefeller Institute have now been treated by the administration of immune serum. The results in the cases treated with serum of type II have not been very satisfactory. This was to be expected from the relatively slight potency of the serum employed. Only a small number of cases, however, have been treated, and at present we are not ready to report on the results. On the other hand, the results obtained in treating a series of cases due to infection with pneumococci of type I with serum of type I have been encouraging. Forty-eight cases have now been treated, and among these four deaths have occurred. Among these four fatal cases, death occurred in one from a pulmonary embolism during convalescence, after he had recovered from the acute pneumonic infection. Two of the other cases were treated only in the latest stages of the disease; in both cases the serum being used only a few hours before death. In only one case can the treatment be said to have been at all efficiently carried out, and even in this case the serum was only administered on the fifth and sixth days, death occurring on the sixth day.

It is perfectly well realized that it is very dangerous to draw conclusions as to the efficacy of any method of treatment in a series of cases of pneumonia unless the number of cases be extremely large, running up into the hundreds, or better into the thousands. However, as the cases treated were, on the whole, very severe ones, and careful bacteriological studies in all these cases were made, the fact that the mortality among these cases was only 8 per cent., as contrasted with 25 per cent. in the untreated cases, is certainly not discouraging, and offers some ground for hoping that the serum treatment in this type of case may prove efficacious. That these cases were severe ones is shown by the fact that the number of positive blood cultures obtained in these cases was larger than in the series of untreated cases, among which the mortality was 25 per cent. The fact that, in cases with positive blood cultures, the bacteria have disappeared from the blood, in all these cases except one, following one dose of the serum, shows that, in any case, the

serum prevents the occurrence of bacteriemia. The method is now being employed to a constantly increasing extent, and the results seem to justify its use, under conditions where accurate determination of type and careful observations of its effect on the patients may be made. When we remember that in New York the number of deaths due to this type I infection alone is greater than all the deaths due to typhoid fever, scarlet fever, and cerebrospinal meningitis combined, it is evident that a method which would lessen the mortality of this type of infection would mark a distinct advance.

CHEMOTHERAPY

Soaps of Unsaturated Fatty Acids. In 1910 Lamar showed that the alkaline soaps of sodium oleate and other unsaturated fatty acids have a marked destructive action on pneumococci. Such soaps cannot be applied therapeutically, but Lamar showed that by using a proper mixture of soap, sodium oleate and immune serum it became possible to increase the action of the immune serum and to cure animals locally infected. Such a method does not seem applicable to a general or deep-seated infection with pneumococcus, but it seems highly probable that it might be effective in local infections, where the mixture could be directly applied.

Ethyl hydrocuprein. The fundamental facts in regard to the specific action of ethyl hydrocuprein or optochin are as follows: Morgenroth has shown that doses of ethyl hydrocuprein, less than the toxic dose for mice, may have a prophylactic effect when injected simultaneously with a multiple of the minimal lethal dose. Second, Wright has shown that the drug has a specific bactericidal action for pneumococci *in vitro*. These effects of this drug are not specific for any one type of pneumococcus. Even Pneumococcus mucosus is susceptible to its action. There are certain facts, however, which must be considered in discussing the application of this drug in the treatment of acute lobar pneumonia. (1) In treating mice it has been found necessary to employ at least 0.5 c.c. of a 2 per cent. solution of the drug given simultaneously with, or very shortly following the infection, 0.4 c.c. of the same solution on the second day, and 0.4 or 0.5 c.c., as may be required, on succeeding days.

The average toxic dose of the drug for 20 gm. mice is about 0.6 to 0.7 c.c. It is thus evident that to obtain results in mice the dose employed is extremely near the toxic one. Second, the infecting dose employed in most curative tests has been a relatively small multiple of the lethal one. If the minimal lethal dose is 0.000001 c.c. of culture, usually the tests have been made with 0.001 c.c., a very small infecting dose as compared with those against which immune serum may be effective.

Lastly, in experimental studies of the drug in mice, the weight of the animal employed is of great importance as regards the protective and curative dose. Since the activity of the drug apparently depends upon its concentration in the body fluids, it is evident that in man and larger animals very much larger doses must be employed. At least 0.01 gram is required to cure a 20 gm. mouse. A proportionate dose for a 70 kg. man would be 35 gm. of the drug. In view of this fact it would seem that the small doses now considered safe in man, namely, three doses per day of 0.5 gm. each, can hardly be expected to have much effect. Larger doses than these administered to man have caused amblyopia. It should be stated, however, that in no case in which the amblyopia was clearly due to the drug were the changes in the eyes permanent. It must be remembered also, however, that in chemotherapy one cannot safely apply the results obtained in one species of animal to the probable results to be obtained in another species, especially as regards dosage. Wright has made observations which suggest that in man, with the smaller doses employed, a sufficient concentration may be obtained to be effective. Further experiments along this line, however, are needed. The total number of cases reported, treated with optochin, is not large. Small series have been treated by different observers. The opinions of these observers as to the efficacy of the drug differ. It is evident that the results are not striking. With the small doses mentioned, apparently no harm is done. Judgment must therefore be deferred as to the efficacy of the drug in pneumococcus infection in man.

It is possible that by a combination of the drug with immune serum the effects of the latter might be increased. This has already been tested experimentally by Engwer and also by Boehncke.

Lenné treated eighteen cases by the combined method with a mortality of 16.5 per cent. Baermann has also tested the therapeutic effect of ethyl hydrocuprein in combination with the serum obtained from patients during convalescence. According to Boehncke the "schwellenwert" of antipneumococcus serum is lowered by the administration of optachin in pulmonary pneumococcus infections in guinea-pigs. These results are suggestive. To justify this method in man, however, it should be shown experimentally that the maximum effect of the serum may be increased by the drug. Experiments in this direction are now being made by Dr. Moore, and the experiments so far indicate that serum plus optochin may protect against somewhat larger doses of pneumococci than serum alone. In case treatment of pneumonia with optochin should prove of value, it indicates great clinical acumen on the part of the physicians who have advised the use of quinin in pneumonia, for this drug, even as compared with optochin, must have an extremely slight effect in this disease. Whatever may be the value of optochin in the treatment of acute lobar pneumonia in man, the first steps in chemotherapy have been taken, and this is of great importance.

In this brief review I have tried to indicate the chief advances which have been made toward a specific treatment of acute lobar pneumonia. The most hopeful indication, however, of the ultimate development of a rational treatment of this disease is that the methods of study are no longer purely statistical and empirical. Most knowledge has been obtained concerning the nature of the disease and the mechanism of recovery and of immunity. Methods have been devised for the accurate experimental study of proposed therapeutic measures, and judgment of their probable effectiveness no longer needs to be based entirely on the mortality percentage in patients treated by a given method.

STUDIES ON THE RELATIONS OF THE HYPERSUSCEPTIBILITY AND INSUSCEPTIBILITY INDUCED IN GUINEA-PIGS BY THE INSTILLATION OF HORSE SERUM INTO THE NOSE[1]

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Evidence that absorption of an antigen through the mucous membrane of the nose may determine a biological response different in degree if not in kind from that of the same antigen injected beneath the skin is presented by the experiments of various observers with diphtheria toxin. Anderson[2] tried in vain to immunize guinea-pigs to diphtheria toxin by subcutaneous injection. "Before an amount (in divided doses) equal to a M.L.D., had been given the animals in each case died." On the other hand, Dzerjgowsky[3] Blumenau[4] and others found no difficulty in producing, in both man and animal, a degree of active immunity to diphtheria by introducing the toxin into the nose.

In work reported by one of us before this Society a year ago, it was shown that when guinea-pigs were treated by a series of instillations of horse serum by the nose and then, sixteen days after the last instillation, were given a large toxic injection by the vein, in certain animals no discernible reaction was produced.

Survival of subsequent intravenous injections showed that the animals had been immunized against horse serum by the instillations.

[1] Abstract of a paper appearing in full in Arch. of Int. Med., 1915, xvi, 605.
[2] Hygienic Lab., 1906, Bull. No. 30.
[3] Zeitschr. f. Immunitätsf. (Abstract), 1910, iii, 602.
[4] Zeitschr. f. Immunitätsf., Ref. Bd., 1911, pp. 196, 353, 860; also, Jahrb. f. Kinderheilkunde, 1911, lxxiv, 141.

It is of fundamental importance to discover the conditions according to which a toxic injection may, after a series of instillations, in one case cause speedy anaphylactic death, in another more or less profound shock, and in a third no perceptible reaction. The present investigation was undertaken to find out whether the effect of the toxic injection was influenced: (1) by the number of times horse serum was instilled into the nose of the guinea-pig, (2) by the interval elapsing between instillations or the rhythm of their succession. The antigen employed was Cutter's normal horse serum and the amount used at each instillation was approximately 0.18 c.c. The guinea-pig being held supine upon a table, the serum was dropped from a hypodermic needle upon one or other nostril. The toxic injections were all given by the vein and the amount of serum used in each was about 0.38 c.c. The first toxic injection was made sixteen days after the last instillation, the second injection twenty-four days later still, and subsequent injections, when given, at longer intervals.

Animals were treated with instillations varying in number from one to twelve. So far as we could determine, a single instillation of serum produced no change in the animal which could be recognized in a reaction to the toxic injection. When two instillations were given, separated by intervals varying from fifteen hours to sixteen days, there was in most cases a plain biological response, for the guinea-pig either quickly succumbed to the toxic injection or showed slight to moderate signs of sensitization. In three out of thirty cases of one group in which but two successive instillations were given, the toxic injections made sixteen days after the last caused no definite disturbance. It might be thought that the negative result depended on a lack of response of the tissues to the serum. That this is not true is proved by the fact that second intravenous injections, given twenty-four days after the first, were likewise withstood, in two cases with moderate reaction and in the remaining with little or none. These experiments demonstrate the development of immunity to the intravenous injection of 0.38 c.c. serum without the evidence of a preliminary stage of anaphylaxis.

The profound effects, either in the direction of sensitization or

protective tolerance, which may be manifested after but two instillations of serum seem to be intensified by repeating the treatments. How far the biologic modification depends upon repetition of the application of the antigen through the nose we have not determined. Five successive instillations may apparently produce a maximal biologic response.

We were possessed with the idea that the nature of the reaction to the toxic injection is influenced or determined by the rhythm of the successive instillations or by the intervals separating them. Forty-one guinea-pigs were divided into groups and treated with series of five, six or twelve instillations at intervals between the instillations of one, two, four, five, six, fourteen and twenty-four days. Of these animals twenty-one died promptly with the toxic injection; of the twenty surviving it, only three showed more than slight anaphylactic response. Only five of the twenty survivors succumbed to the second toxic injection given twenty-four days later. How long the biologic change induced by the nasal instillations endures we are not prepared to say. In a group of three animals in which the toxic injection was withheld for forty days after the last instillation, two died and one survived with slight reaction; therefore both the anaphylactic and the protective effects of the instillations endure at least forty days. Other experiments were conducted in which five instillations were grouped in various ways; but all of our results may be briefly summarized in the statement that neither the interval separating regularly spaced instillations nor the rhythm with which these succeeded one another influenced in any certain manner the nature of the reaction to the toxic injection. It is worth noting that a special inquiry into the question as to whether the negative response to a toxic injection might not be due to a condition of "antianaphylaxis" was answered decidedly in the negative. In guinea-pigs treated with a series of instillations of horse serum by the nose, occasionally one will develop a specific reaction in the form of a typical bronchial asthma with abundant moist rales emanating in order, apparently, from the nose, the trachea and the bronchi. Such animals always quickly succumb to the toxic injection. In normal pigs the reaction described first occurs with an instillation given eight days or more

after the first. It is probable that by giving three or four instillations of 0.2 c.c. serum at twenty-four-hour intervals and then repeating, after a lapse of two weeks, the experimental asthma may be nearly always induced. The phenomenon is apt to be caused more readily and after a shorter latent period in guinea-pigs previously thoroughly sensitized by subcutaneous injection.

It seems to be the consensus of opinion that guinea-pigs serum-immunized according to the ordinary methods of injection gradually lose their resistance to the antigen. Thus, Gay and Southard lay stress on their findings that animals rendered "immune," usually by large spaced injections of serum, acquire sensitivity and "eventually become quite as susceptible as do animals which have had a small initial dose, the incubation period varying directly with the amount injected on the first dose or doses. It seems more correct, then to refer to these animals as 'refractory' rather than 'immune.' It was furthermore noted that the offspring of such refractory animals, born during a period of full refractoriness in the mother, were not themselves refractory, but sensitive to intoxication by horse serum."[1]

Wholly different conclusions must be drawn from our results with guinea-pigs immunized through the nose. The evidence is that with the lapse of time resistance may increase so that much larger doses of serum can be withstood than at an earlier date. Thus, a group of three pigs which had received six instillations of serum at intervals of fourteen days, were given intravenous injections of 0.38 c.c. serum sixteen and forty days after the last instillation, with varying degrees of anaphylactic response. Seventy-five days later still the same injection was withstood without symptoms. One of the animals was given a fourth intravenous injection thirty-six days after the third i. v. but the quantity of serum was increased to more than 1 c.c., nearly three times the usual toxic dose. The pig survived after a very severe reaction. The other two animals were kept for one hundred and one days after the third injection when they received a still larger i. v. i. of just three times the usual quantity. This they survived with scarcely perceptible reaction. Other experiments point in the same direction.

[1] Gay and Southard, Jour. Med. Res., 1908, xviii, 407.

Also, the offspring of certain of our "immunized" guinea-pigs showed marked resistance to the toxic injection of horse serum. This was most striking in the case of the offspring of mothers which had been treated by nasal instillations only early in their period of gestation. Of seven of such offspring from four different mothers, five survived the toxic injection of 0.25 or more of serum given nineteen to thirty-three days after birth.

Some of our highly refractory animals were bled and their centrifuged sera were injected at once, in varying amounts, into the peritoneal cavities of normal young pigs, which themselves were tested as to passive sensitization by intravenous injection of serum one to two days later.

Of twelve normal pigs so treated none died with the intravenous injection of 0.25 serum and most of them showed little or no anaphylactic response. The amounts of serum used to confer passive sensitization varied from 0.5 c.c. to 9 c.c. The strongest reactions to the toxic injection were given by the animals which had received but 0.5 c.c. This difficult subject is still being pursued and no deductions will be made at present.

Our results suggest in a very definite way that at least two reaction bodies are concerned in immunization; (1) the familiar *allergin* whose province seems to be the destruction of antigen, with the incidental formation of exceedingly poisonous products. (2) a wholly protective body, which may tentatively be called *antiallergin*, which in some way prevents the development of anaphylaxis.

THE RELATIONSHIP OF CHRONIC PROTEIN INTOXICATION IN ANIMALS TO ANAPHYLAXIS[1]

By WARFIELD T. LONGCOPE, M.D.
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THE experiments which furnish the subject of this paper represent a continuation of some observations made upon the effect of repeated injections of foreign protein in animals sensitized to these specific proteins.[2] Under these conditions areas of degeneration with extensive inflammatory reaction are produced in the myocardium, the liver, and the kidneys. In different species of animals the effects vary somewhat, since the kidney is involved in the dog, cat, and rabbit and guinea-pig, the liver in the rabbit and cat,[3] and the myocardium[4] in the rabbit and guinea-pig. A detailed description of these changes has already been published, and it is, therefore, necessary only to state that they consist in focal areas of degeneration, infiltrated with small round cells, which in the heart are scattered throughout the myocardium of both ventricles, in the liver are usually situated about the portal spaces, and in the kidney are seen most often through the mid zone, whence they extend into the cortex. In their most advanced stages these alterations produce the picture of an extensive myocarditis, a periportal cirrhosis of the liver, or a widespread subacute nephritis with involvement, at times, of the glomeruli.

At first it was thought that sensitization to some foreign protein, as horse serum or egg white, was necessary before subsequent

[1] From the Medical Clinic of the Presbyterian Hospital, Columbia University, New York.

[2] Longcope, Jour. Exp. Med., 1913, xviii, 678.

[3] Ibid., Trans. Assn. Amer. Phys., 1913, xxviii, 497.

[4] Ibid., Arch. Int. Med., 1915, xv.

injections of the same protein could bring about the development of such changes, but further study showed that similar though less marked alterations might occur in animals receiving but a single large dose of horse serum or egg white. The question, therefore, arose as to whether the effects produced were the result of introducing repeatedly into the bodies of these animals small quantities of a substance which was in itself primarily toxic for the cells of the kidneys, liver, and myocardium, or whether the horse serum and egg albumen became injurious only after the animals were sensitized to these substances. In the latter case the subacute inflammatory reactions might readily be dependent upon the repeated anaphylactic shocks to which the animals were subjected.

Though a number of observers interested principally in the fact that egg white when introduced parenterally into animals is eliminated as such in the urine, have studied casually the kidneys of animals soon after an injection of egg white, very few have described definite alterations in the kidneys. Bridge Adams[1] and Maschke[2] state that the kidneys of rabbits after single injections of egg white are normal. Sollmann and Brown[3] observed under the same conditions occasional swelling and degeneration of the tubular epithelium. Chiray[4] could not discover any changes in the kidneys of rabbits after a single intravenous, intraperitoneal or subcutaneous injection of egg albumen but noted after repeated injections, which were limited to a few animals, degeneration of the tubular epithelium with cellular reaction and scar formation that led to chronic nephritis.

The following experiments were undertaken with the view of determining, if possible, whether the toxic action of horse serum and egg white was a primary property of these proteins or developed only when the animals were sensitive to such foreign proteins. The latter view would express the idea which has long been held by Vaughan.[5]

[1] Inaug. Diss., Leipzig, 1880.
[2] Berl. klin. Wchnschr., 1912, xlix, 145.
[3] Jour. Exp. Med., 1902, vi, 207.
[4] Thèse, Paris, 1906.
[5] Protein-split Products in Relation to Immunity and Disease, 1913.

It was thought that if the protein itself were toxic it might be possible to demonstrate this toxicity by injecting repeatedly at weekly intervals, proteins always of a different type, so that the animal might receive large quantities of foreign protein but never the same protein twice, thereby avoiding anaphylactic shock.

The following experiment was, therefore, performed: Four lots of rabbits were selected from a single stock. Lot A consisting of eleven rabbits, was used as control. Lot B consisting of eleven rabbits was sensitized to horse serum or egg white by intraperitoneal inoculation of 2 to 4 c.c. of these proteins on three consecutive days. After an interval of several weeks they were reinoculated intravenously at weekly intervals with horse serum in amounts varying from 0.5 to 6 c.c. or with egg white in amounts varying from 0.4 to 0.8 c.c. Lot C, consisting of nine rabbits, was injected intravenously at weekly intervals with horse serum, egg white, beef serum, sheep serum, dog serum, cat serum, human serum, pig serum, edestin, and casein. The edestin and casein were made up in 2 per cent. solution in Na_2CO_3. The proteins were given in doses of 1 c.c. to the kilo body weight, the actual dose varying from 1.0 to 2.7 c.c. It was so arranged that the total amount of serum, etc., which each rabbit in this group received was as great or greater than that given to the animals in group B.

Finally, in lot D a series of seventeen rabbits was given each a single dose of horse serum or egg white, either intravenously or intraperitoneally, and killed at intervals varying from three to twenty-nine weeks. Five of these received 2 c.c. of egg white intraperitoneally. Four received 2 c.c. of horse serum intravenously and one rabbit 1 c.c. of horse serum intravenously; two rabbits received 2 c.c. intraperitoneally and one rabbit received 1 c.c. intraperitoneally; one received 3 c.c. and 1 received 5 c.c. of sheep serum intravenously; one rabbit received 6 c.c. of dog serum intravenously and one received 6 c.c. of cat serum intravenously.

In order to eliminate any possible effect which fresh serum might have, the sera for all these experiments were heated for one-half hour at 56° C.

The following table gives the results of these experiments:

TABLE I

	Lot A. Normal control rabbits uninoculated.	Lot B. Rabbits sensitized to egg white or horse serum and after three weeks reinjected with egg white or horse serum.	Lot C. Rabbits receiving repeated inoculations of different proteins (horse serum, egg white, beef, sheep, dog, cat, human, and pig serum, edestin, and casein).	Lot D. Rabbits receiving a single dose of foreign protein.
Number of rabbits	11	9	9	17
Number of intoxicating doses	0	2 to 10	1 to 10	1
Involvement of myocardium	0	9	3	7
Involvement of liver	0	9	1	4
Involvement of kidneys	1	9	3	12
Total animals	11	9	9	17
Total positive	1	9	3	12

The uninoculated control rabbits (lot A) all showed normal organs except one. In this one rabbit a few areas of round-cell infiltration were seen in the pelvis of the kidneys.

Of the eleven sensitized rabbits in lot B, two died before intoxicating doses of protein were administered. They showed normal organs. The nine sensitized rabbits receiving subsequent injections of serum all showed extensive and advanced changes in the heart muscle, liver, and kidneys.

In lot C, only one-third of the animals developed changes in one or the other of these organs, and these were much less extensive than the lesions appearing in lot B.

In lot D, where the animals received but a single inoculation of egg white or horse serum, the results corresponded quite well to those observed in lot C.

It is, therefore, evident that though previous sensitization increases the incidence and severity of the changes it is not necessary for their development.

During further experiments it was noted that when alterations occurred in the internal organs after a single inoculation they did not make their appearance for several days after inoculation. Experiments were, therefore, designed to determine more accurately the time of appearance of these lesions and to determine why this

should be so long delayed. If the lesions were dependent upon the introduction of a toxic substance, one would expect, especially when the toxin was given in large amounts, that it would act much more promptly.

It is well known that the skin of an animal sensitized to a foreign protein such as horse serum will react specifically to the intracutaneous injection of that protein. In rabbits this specific sensitiveness of the skin usually develops within ten to twenty days after the primary inoculation of horse serum, and as Knox, Moss, and Brown[1] have shown, manifests itself, after the intracutaneous injection of minute quantities of serum, by the appearance in twelve to thirty-six hours of a large area of reddening, swelling, and edema which persists at the site of inoculation for twelve to twenty-four hours. According to the view which generally prevails the reaction is associated with the union of the antigen (horse serum) with antibodies formed against this specific protein.

This method was, therefore, utilized to determine whether or not the lesions in the internal organs following a single inoculation of horse serum were associated with the appearance of skin sensitiveness, and therefore probably with the development of antibodies toward horse serum in the body of the animal.

It was at first hoped that repeated intracutaneous injections of horse serum, in amounts varying from 0.02 to 0.1 c.c. might be made, in order that the exact time at which sensitiveness developed could be fixed, but in normal rabbits used as controls the repeated intracutaneous injections at four to six days' intervals, of horse serum even in such small amounts, led eventually to a positive reaction, which was interpreted as a true "Arthus phenomenon." In such animals, however, general sensitiveness did not develop, since the injection of large quantities of horse serum intravenously in animals giving a positive skin test did not produce symptoms of anaphylaxis. In view of this fact it was possible to use the intracutaneous test only once.

For the final experiment fifteen white rabbits were injected intravenously with from 5.5 to 9 c.c. of horse serum in divided doses

[1] Jour. Exp. Med., 1910, xii, 562.

during three consecutive days. At varying intervals after the first dose an intracutaneous injection of from 0.02 to 0.05 c.c. of horse serum was made on one side of the shaved abdomen, while an equal amount of sheep or beef serum was injected in the skin of the opposite side as a control. The animals, except in one instance, were observed for from thirty-six to forty-eight hours, and after the result of the skin test had been noted, killed, carefully autopsied, and their organs examined histologically.

The result of this experiment is given in Table II.

TABLE II.—ASSOCIATION BETWEEN DEVELOPMENT OF LESIONS IN HEART, LIVER, AND KIDNEYS AND APPEARANCE OF SKIN SENSITIVENESS IN FIFTEEN RABBITS RECEIVING SINGLE INJECTIONS OF HORSE SERUM

Rabbit No.	Amount of serum.	Lived after injection.	Skin reaction.	Heart.	Liver.	Kidney.
15	5.5 c.c.	7 days	Not made	0	0	0
9	8.5 c.c.	8 "	" "	0	0	0
17	5.5 c.c.	8 "	+	0	0	0
10	8.5 c.c.	10 "	+	0	+	++
7	8.5 c.c.	12 "	−	0	0	0
8	8.5 c.c.	12 "	+	0	0	+
11	5.5 c.c.	13 "	Not made	0	0	0
5	8.5 c.c.	14 "	−	0	0	0
6	8.5 c.c.	14 "	+	0	+?	0
13	5.5 c.c.	17 "	+	0	0	+
16	5.5 c.c.	21 "	−	0	0	0
18	5.5 c.c.	22 "	−20 hours	+	+	++
12	5.5 c.c.	27 "	++	++	+	0
1	8.0 c.c.	30 "	++	+	+	++
2	9.0 c.c.	30 "	+	+	++	+
19	0	Control	.....	0	0	0
20	0	"	.....	0	0	0
4	0	"	+ pure Arthus	0	0	0

It will be seen that from the seventh to the twenty-first day after inoculation there were occasionally observed scattered and slight changes in the liver or kidney. When such alterations were found during this period they always occurred in rabbits that gave a positive skin test. All animals that gave a positive skin test, however, did not show changes in the internal organs.

After the twenty-second day the incidence and extent of the changes in the internal organs increased greatly and the skin reaction, except in one animal, was very intense. Uninoculated controls and one animal subjected to intracutaneous inoculation alone, showed no changes in the internal organs.

Table II shows very well that the lesions in the internal organs appear either at the time the skin sensitiveness has made its appearance or directly afterward, and therefore, after the animal has, hypothetically, produced antibodies to the foreign protein. One may liken the condition to serum disease in man during which time profound and very obvious disturbances may take place. In the rabbit the signs and symptoms so characteristic of the disease in man are lacking, though in one or two of the rabbits in this series moderate subcutaneous edema and generalized enlargement of the lymph nodes was observed at autopsy. von Pirquet and Schick[1] have noted under the same conditions in rabbits alterations in the total and differential leukocyte counts that are analogous to those that are observed in children during serum sickness. The effect of anaphylactic shock, is, however, so unlike in different species of animals that it is not permissible to draw general conclusions from the results obtained in any one species.

Conclusions. Such foreign proteins as horse serum and egg white in the amounts employed in these experiments do not produce evidences of intoxication immediately after injection into rabbits. Single large injections do, however, produce changes in the parenchymatous organs after a period of ten to twenty-one days. These develop at the time or immediately after the animal has formed antibodies for the foreign proteins.

The mechanism of the development of the lesions in the myocardium, liver, and kidneys of rabbits is thus the same whether a single inoculation is given or whether repeated inoculations are made in sensitized animals. By the latter method, however, much more marked and extensive changes may be produced.

[1] von Pirquet und Schick, Die Serumkrankheit, Leipzig, 1905.

STUDIES OF NEPHRITIS[1]

By HENRY A. CHRISTIAN, M.D., CHANNING FROTHINGHAM, Jr., M.D., JAMES P. O'HARE, M.D., AND ALAN C. WOODS, M.D.

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During the past year and a half in the medical clinic of the Peter Bent Brigham Hospital we have been studying cases of chronic nephritis from several angles. Some of these studies have been published, others are ready for publication, while still others are incomplete. All these studies are more or less closely related to each other and form part of a somewhat systematic investigation of nephritis. Different members of the staff have taken up the study of special phases of the subject, and from time to time each has published the study which he has made. What we will present here represents part of our recent work. The several names that appear under the title are those of the men responsible for the work which is outlined here. In more detailed form each man will publish subsequently under his own name his own work.

A. Test Renal Meals in Relation to Renal Function. The ability of the kidney to excrete certain factors in the average normal diet has been utilized by many as a means of measuring renal function. The excretion of water, sodium chloride, and nitrogen has been tested by most observers. One method suggested by v. Monakow[2] has been to place the patient upon some form of diet which contains daily approximately the same amounts of sodium chloride, nitrogen, and water with a caloric value varying but little from day to day. In relation to this diet the twenty-

[1] From the Medical Clinic of the Peter Bent Brigham Hospital.
[2] Deutsch. Arch. f. klin. Med., 1911, cii, 248.

four-hour amount of urine and its sodium chloride and nitrogen content have been quantitated. Then on different days these patients have received, in addition to the diet, 20 gm. of urea or 10 gm. of sodium chloride, and the ability of the kidney to excrete these added amounts of nitrogen and sodium chloride has been determined.

As in this test it is necessary for the patient to reach a certain degree of equilibrium of excretion after the diet has been begun before the added salt and nitrogen can be given, and as it is necessary to observe the excretion of these substances for at least two days after each is given, and as it is usual to allow the effect of the added amount of the one to end before adding the other, to carry out this test satisfactorily requires about ten days of accurate dieting with the patient in the hospital.

In 1914 Hedinger and Schlayer[1] published a paper in which the effect of diet on the excretion of water and sodium chloride was studied by submitting the patient for one day to a diet in which different meals contained varying amounts of water, sodium chloride, and nitrogen.[2] The urine was collected in two-hour periods through the day, and the water and sodium chloride were quantitated in each two-hour amount. The test renal meal day was preceded by two days on which the patient was on a light mixed diet containing from 8 to 12 gm. of NaCl, and with a fixed quantity of fluid, and on these days merely the excretion of water in relation to fluid intake was measured.

This form of test renal meals requires three days of the patient's stay in the hospital, but only on one day is accurate dieting necessary. The question naturally arises. Can as much information be obtained from the one test as from the other? If so, the shorter period of time required for the test of Hedinger and Schlayer would have a manifest advantage. During the past year we have investigated this question. We have modified the test as proposed by Hedinger and Schlayer by quantitating the nitrogen in the various portions as well as the water and sodium chloride, and we

[1] Deutsch. Arch. f. klin. Med., 1914, cxiv, 120.

[2] In these meals the content of each also varied in food substances having a diuretic effect (water, salt, purins, etc.)

have changed slightly the composition of the meals on both the test day (Chart I) and on the two preceding days.[1]

Without entering at this time into any discussion as to the value of such test renal meals in determining the renal function, we will discuss comparatively the results obtained in the two forms of tests carried out on the same patient. On sixteen patients with chronic

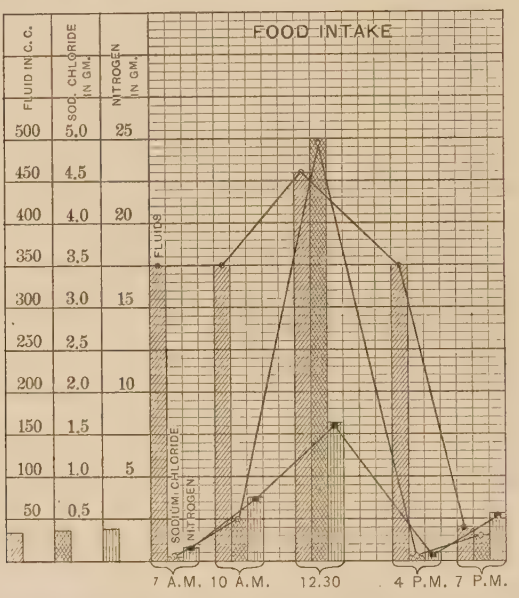

CHART I.—To show amounts of fluid, sodium chloride, and nitrogen in each meal of the renal diet. The lines connecting the tops of the columns give the curve of variation in intake of each constituent.

nephritis both tests were carried out in a complete form. In addition to these patients a variety of other methods of testing renal function were applied. In an equal number of cases only the

[1] On the test day we have used the following menu for the several meals:

7 A.M. Coffee, milk, sugar, toast, and butter.

10 A.M. Milk, toast and butter.

12.30 P.M. Bouillon, broiled steak, butter, mashed potato, butter, toast and butter, coffee, milk and sugar.

4 P.M. Tea, milk, sugar, crackers.

7 P.M. Soft egg, blanc mange (one egg, sugar, corn starch, milk) cream, in amount to give approximately total calories 2500, total fluids, 1550 c.c., total protein 76 gm., total fats 127 gm., total carbohydrates, 245 gm., total sodium chloride, 5.8 gm. On the two days preceding the test day the patient usually has a diet containing 2000 calories, 75 gm. of protein, and 4 gm. of sodium chloride.

Hedinger and Schlayer test renal meal method was applied in connection with other forms of renal functional tests. The results of all of these tests from the point of view of estimating the function of the kidney and the relative value of each will be discussed by Dr. O'Hare when he publishes a detailed statement of this work.

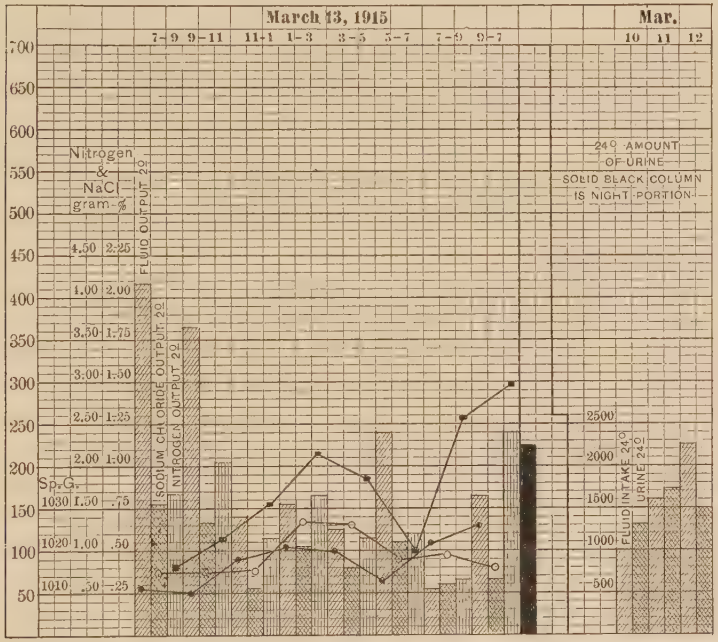

CHART II, Case I.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M., and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

We have found that these two forms of testing renal function in relation to test diets agree quite well in their results. (Case I, Chart II and III; Case II, Chart IV, and V; Case III, Chart VI and VII; Case IV, Chart VIII and IX). That the results very closely agree in any quantitative sense is, of course, not to be expected, for we have found that if we gave added salt or added urea on several occasions to our patients on a standard diet the

results obtained are rarely quantitatively identical, but there is generally a striking similarity in the results from period to period. (Charts VII and XII.)

In the same way we have repeated the Hedinger and Schlayer test renal meal on the same patient and found very considerable variations in the curve of excretion of the various components which were quantitated (Case V, Charts X and XI), but at the

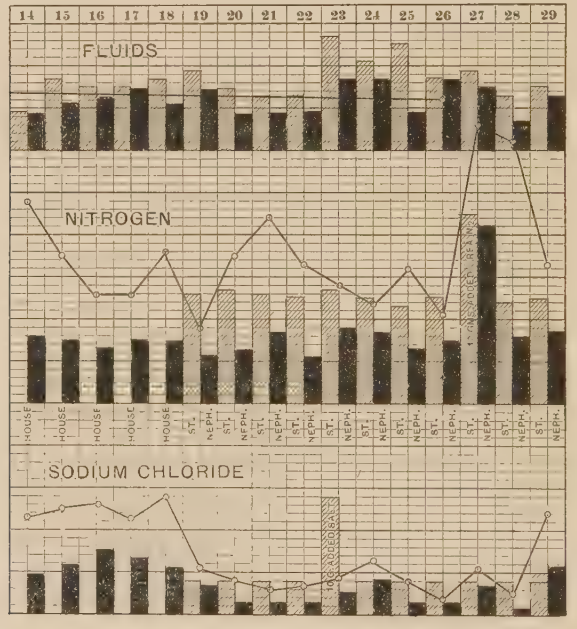

CHART III, Case I.—The hatched columns indicate intake; the solid columns output. The upper series are for fluids, the middle for nitrogen, and the lower for sodium chloride. The added salt and added urea are indicated by the lengthening of the columns of intake.[1]

same time there is enough similarity in the different periods to justify the same conclusions as regards the ability of the kidney to excrete the various components when no extraneous factors in the interval between the tests had come in to alter the character of the result.

[1] "House" indicates a general mixed diet; "St. neph." indicates a diet of about 2000 calories, containing 75 gm. of protein and 4 gm. of sodium chloride.

Perhaps there has been a somewhat closer agreement between the two tests in regard to the salt excretion than has been found in the nitrogen excretion. It has been our experience that the ability of the kidney to excrete salt is decreased much earlier than is the case with nitrogen, and many more of our cases have shown an inability to excrete salt well than has been the case with the nitrogen. This

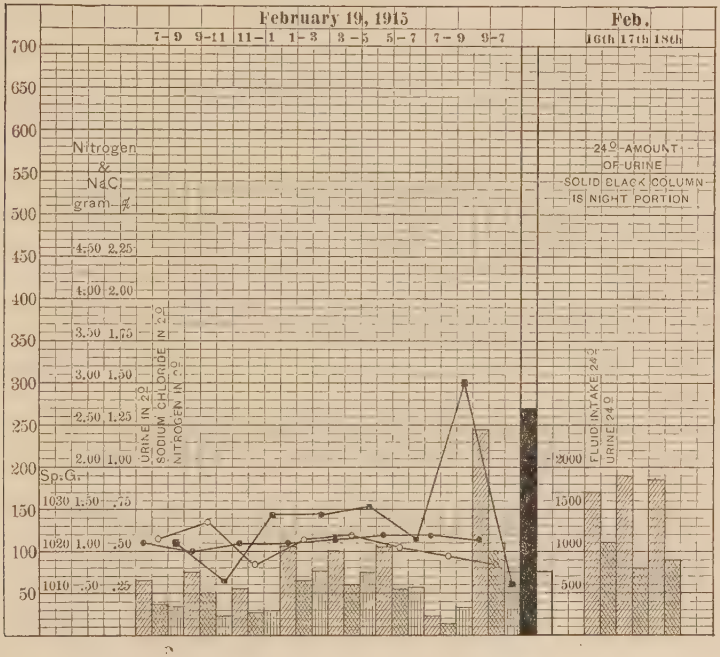

CHART IV, Case II.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M., and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

may possibly explain the greater variation in the results with the nitrogen in these cases which we have studied.

The cases with advanced nephritis, as judged by other tests and the general condition of the patient, by the Hedinger and Schlayer test diet show strikingly a tendency to fixation in the concentration of the urine as measured by the specific gravity, with a relatively

slight variation in the amount passed in each two-hour period. In some cases this fixation in specific gravity has occurred at a low level (Chart VIII) and in others at a fairly high level (Chart IV). In the same way some patients have shown but slight variation in amount of their urine from period to period with either a very small amount or a fairly large amount in each period. Fixation of salt concentration has occurred in the more severe cases and

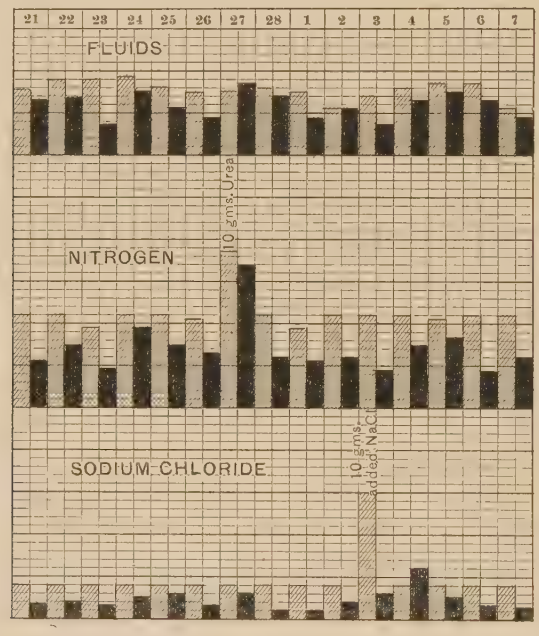

CHART V, Case II. — The hatched columns indicate intake; the solid columns output. The upper series are for fluids, the middle for nitrogen, and the lower for sodium chloride. The added salt and added urea are indicated by the lengthening of the columns of intake.

usually at a low level of excretion. In the longer test, with added salt and added urea, the fixation of specific gravity and the lack of variation in the quantity of the urine is not so apparent.

The inability of the kidney to satisfactorily excrete salt is shown in both tests (Charts VI, VII, VIII, and IX). The same things are true with regard to the nitrogen (Charts VI, VII, VIII, and IX), though there has been less tendency to either fixation in the concen-

tration of the nitrogen or constancy in the amount of nitrogen in each two-hour period.

Both forms of dietary renal tests are of limited application in the sense that cases of severe nephritis often are unable to take the diet on account of lack of appetite or developing nausea. In each form of test the amount of laboratory work is approximately the same. The only distinct advantage of the one over the other is in the shorter period required for the Hedinger and Schlayer test. It is to be

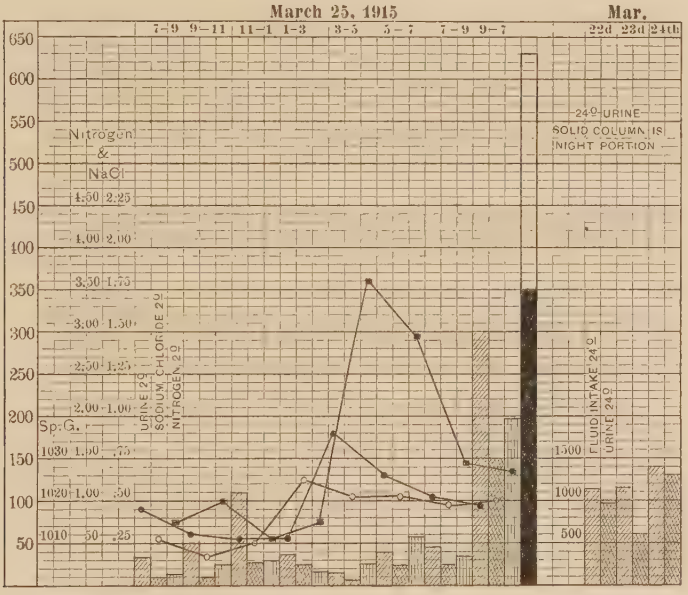

CHART VI, Case III.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M. and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

remembered that not exactly the same form of test is being applied, because in the one the chief factor in the test consists in seeing what the ability of the kidney is to excrete a single substance added to a diet containing only a moderate amount of that given substance along with other constituents. In the other test the excretion of

several substances contained in a varying admixture of food constituents is being studied over a much shorter period of time. It might be that the results from the two kinds of tests would be more nearly comparable if in the longer test both added nitrogen and added sodium chloride were introduced into the diet on the same day.

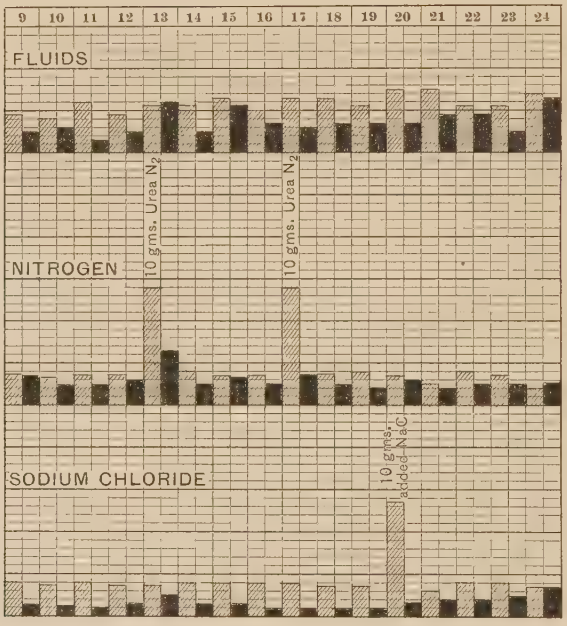

CHART VII, Case III.—The hatched columns indicate intake, the solid columns output. The upper series are for fluids, the middle for nitrogen, and the lower for sodium chloride. The added salt and added urea are indicated by the lengthening of the columns of intake.

In the Hedinger and Schlayer test the results in a case of nephritis cannot be compared in any quantitative sense with what might be termed a normal curve of excretion. Normality consists with this diet in the ability to vary from period to period the amount of water, its specific gravity, the amounts of salt and nitrogen and their percentage concentration rather than to show any definite type of curve of excretion of each. Abnormality consists in a more or less degree of fixation in all of these values or in certain ones of them.

Our general feeling has been that a study of the salt and nitrogen excretion by means of test diets is relatively of less use in determining the prognosis than are some of the other functional tests, such as the phenolsulphonephthalein excretion and the amount of blood nitrogen. This is not because the severe cases fail to show quite definite changes in their excretion, but because the other tests

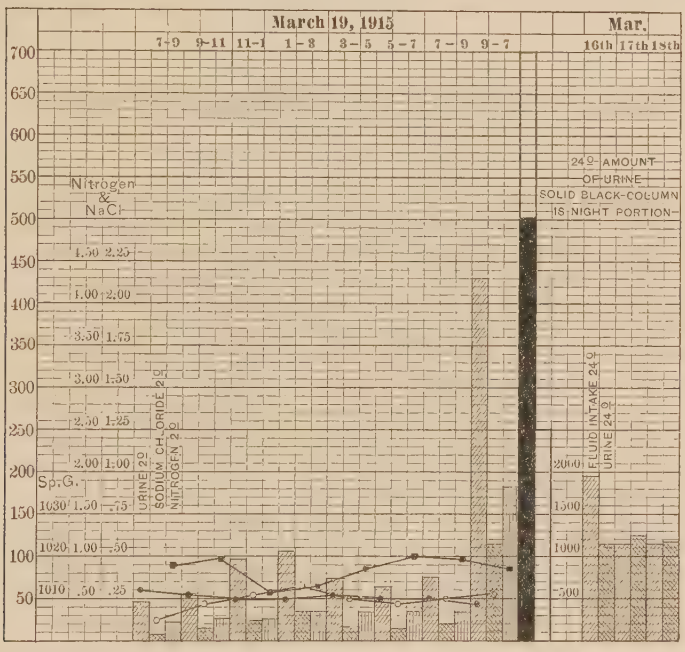

CHART VIII, Case IV.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M., and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

give fully as much information at a much less cost of labor and time. In the milder cases where phenolsulphonephthalein excretion is fair and blood nitrogen low in amount, disturbances in excretion of water, salt, or nitrogen are found; the correct interpretation of this cannot be given until time enough has elapsed to show how these cases progress.

With regard to anatomical diagnosis, we think that a study of salt nitrogen, and water excretion will give very little aid. They serve to subdivide cases of chronic nephritis in a functional sense; the value of so subdividing the cases remains to be shown.

B. Quantitative Studies of Non-protein Nitrogenous Bodies of the Blood. In a series of eighteen patients (Charts XIII, XIV, and XV) with nephritis the total non-protein nitrogen

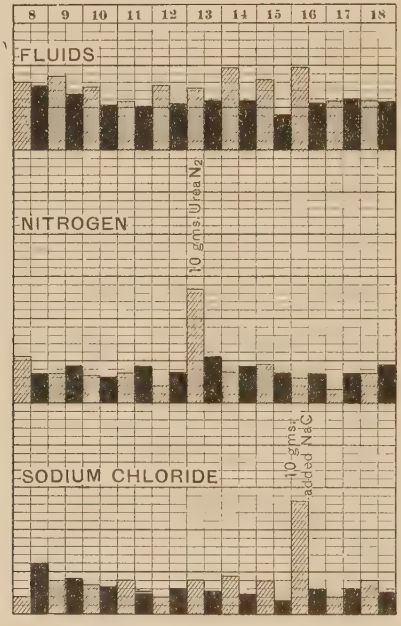

Chart IX, Case IV.—The hatched columns indicate intake, the solid columns output. The upper series are for fluids, the middle for nitrogen, and the lower for sodium chloride. The added salt and added urea are indicated by the lengthening of the columns of intake.

of the blood was determined and also the ammonia nitrogen, urea nitrogen, uric acid nitrogen, creatinin, and combined creatinin and creatin nitrogen, and in most of the cases the amino-acid nitrogen. It was found in this series that the urea nitrogen increased usually in proportion as the total non-protein nitrogen increased and averaged 63.4 per cent. of the total. Ammonia nitrogen increased slightly as the total non-protein nitrogen rose, but this

rise was not proportional. Creatinin showed roughly a proportionate increase while amino-acid nitrogen showed no constant increase. Uric-acid nitrogen increased only very slowly, with an increase in total non-protein nitrogen, and the increase was not regular or proportionate to that of the total non-protein nitrogen.

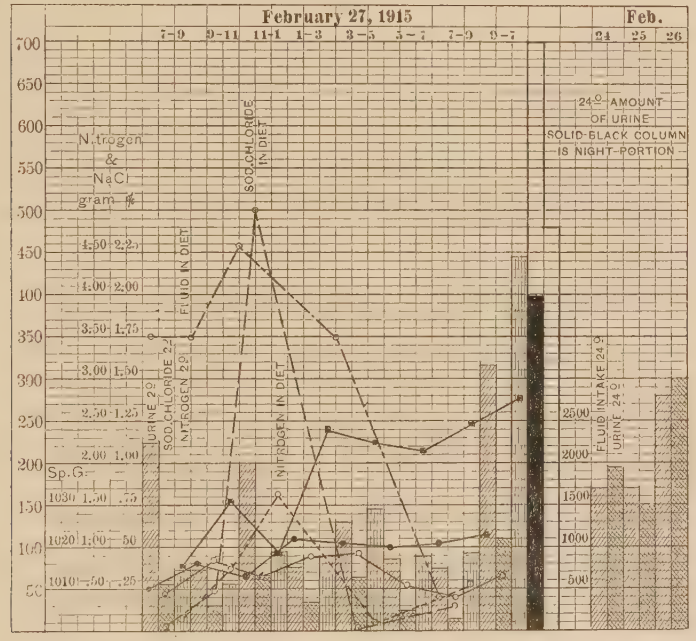

CHART X, Case V.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M., and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day. The broken lines joining dots indicate the amounts of fluid, sodium chloride, and nitrogen in each meal. In the case of nitrogen in the meals the scale is not the same as that of the nitrogen in the portions of urine, but is greater, corresponding to the scale in Chart I.

In those cases (14) in which amino-acids were quantitated the sum total of urea, ammonia, uric acid, creatinin, creatin, and amino-acid nitrogen was subtracted from the total non-protein nitrogen to give a figure for residual or unknown nitrogen. It has been pointed out by others that such a nitrogen portion might contain

the toxic element in nephritis, and so should be largest in those cases with most evident toxemia. In our figures it was roughly proportionate to the clinical severity of the case. However, it is quite evident that summation of errors in individual determinations may be responsible in part for the amount of residual nitrogen. Furthermore, if there is a marked retention of non-protein substances

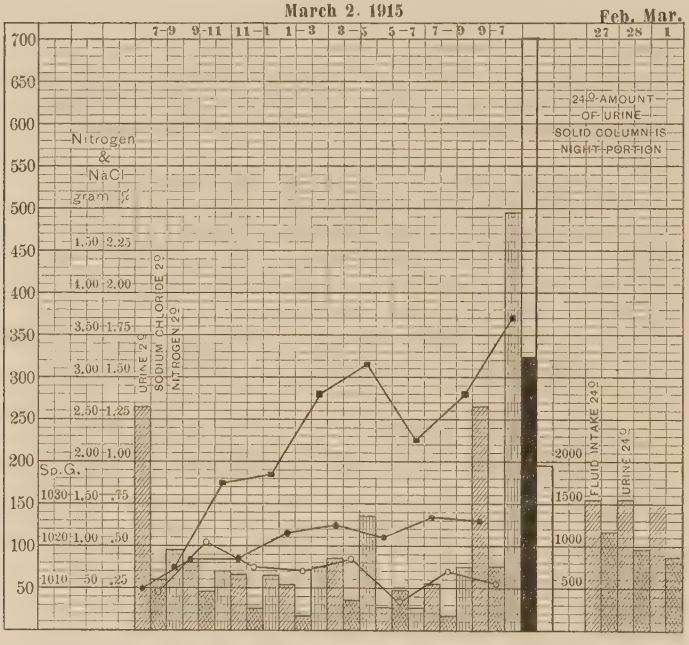

CHART XI, Case V.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M., and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

it is probable that other substances known to be non-toxic not quantitated in our work may have caused all this increase, and the figure means only what a rise in total non-protein nitrogen means.

In these same cases the total non-protein nitrogen and the urea nitrogen of the spinal fluid were determined. With the exception of two cases with anuria (Cases VIII and IX, Chart XII) the total

non-protein nitrogen of the spinal fluid averaged about 25 per cent. lower than that in the blood, while the urea nitrogen in each had almost identical values. It would seem from this that urea is the only one of the nitrogenous bodies readily excreted into the spinal fluid, and that quantitation of spinal fluid nitrogen adds but little information to that obtained from quantitations of blood nitrogen.

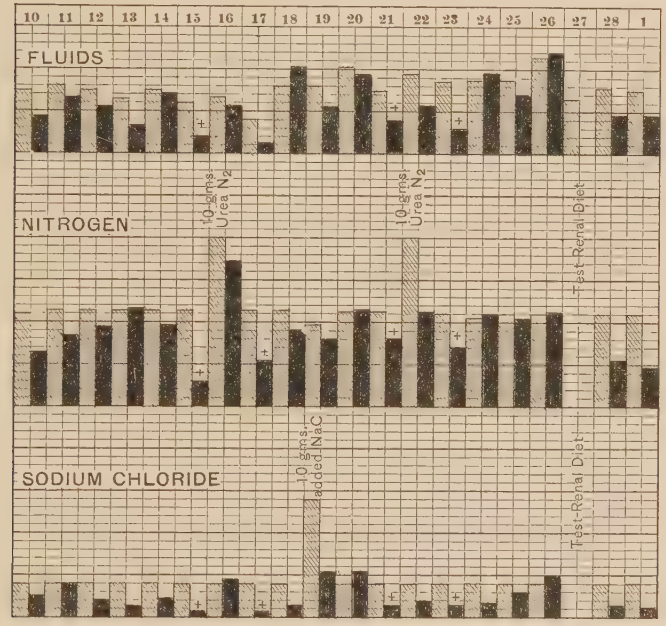
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 1
FLUIDS
NITROGEN
10 grms. Urea N_2
10 grms. Urea N_2
Test-Renal Diet
SODIUM CHLORIDE
10 grms. added NaC
Test-Renal Diet

CHART XII, Case V.—The hatched columns indicate intake, the solid columns output. The upper series are for fluids, the middle for nitrogen, and the lower for sodium chloride. The added salt and added urea are indicated by the lengthening of the columns of intake.

In all of these patients the condition of the retina was carefully studied. It was found that albuminuric retinitis occurred at any level of nitrogen retention, and there was no relation between its occurrence and the proportionate amount of any of the nitrogen bodies quantitated. Certainly, there was found no evidence of a causal relation between any of these nitrogenous bodies and albuminuric retinitis.

C. Diuresis in Relation to Diuretics. From our clinic have been published several papers on the effect of diuretic drugs on animals with experimental nephritis.[1] All together these have shown that the ordinary diuretics are either ineffectual or harmful to animals with these acute renal lesions. The results of these experiments have made us skeptical as to the benefit of diuretic drugs in human nephritis, and so we have been examining our records of patients to see if this skepticism was justified or not.

For some time it has been the routine custom on the medical service of the Peter Bent Brigham Hospital to measure and chart both the fluid intake and urine output of all patients. From these observations an idea may be obtained of diuresis in the average types of cases such as are admitted to a general hospital. Any patient in whom the urine output in twenty-four hours was 1600 c.c or over is regarded as having a diuresis; furthermore, any patient in whom the urine output in twenty-four hours exceeds the fluid intake is considered to have a diuresis. Diuresis in this sense occurred on at least one day in about 15 per cent. of 600 successive patients. Of the 89 patients among these 600 who showed diuresis, the largest group, 32, were cases of chronic cardiac disease, with decompensation in which, with digitalis, limitation of fluid intake and rest, diuresis followed. Next in order came cases of chronic nephritis, 22 in number. Diuresis in this group will be discussed more in detail later. Six patients had diabetes and seven typhoid; in both, diuresis was due to increased fluid intake. The others were miscellaneous cases in which it was often difficult to even surmise as to the direct cause of the diuresis. In this group are patients with diuresis during convalescence from pneumonia and from attacks of bronchial asthma; patients with Hodgkin's disease, general carcinomatosis of the long bones, carcinoma of the head

[1] Christian, Diuretic Drugs in Acute Experimental Nephritis, Jour. Amer. Med. Assoc., 1913, lxi, 267. Chrisitian and O'Hare, A Study of the Therapeutic Value of a Diuretic (Theobromin Sodium Salicylate) in Acute Experimental Nephritis, Arch. of Int. Med., 1913, xi, 517. Walker and Dawson, The Effect of Diuretic Drugs on the Life of Animals with Severe Acute Nephritis, Arch. Int. Med., 1913, xii, 171. Christian, The Effect of Theobromin Sodium Salicylate in Acute Experimental Nephritis as Measured by the Excretion of Phenolsulphonephthalein, Arch. Int. Med., 1914, xiv, 829. Fitz, The Immediate Effect of Repeated Doses of Theobromin Sodium Salicylate and Theocin on Renal Function in Acute Experimental Nephritis, Arch. Int. Med., 1914, xiii, 945.

CHART XIII.—TABLES SHOWING DETERMINATIONS OF NITROGENOUS BODIES IN BLOOD AND SPINAL FLUID IN CASES OF CHRONIC NEPHRITIS WITH NORMAL EYE-GROUNDS

No	Hosp. Med. No.	Blood. Total non-protein nitrogen.	Urea nitrogen.	Ammonia nitrogen.	Uric acid nitrogen.	Creatinine nitrogen.	Creatine nitrogen.	Amino acid nitrogen.	Residual nitrogen.	Chlorides in gms.	Spinal fluid. Total non-protein nitrogen.	Urea nitrogen.	Blood pressure.	Phthalein excretion in 2 hours.	Remarks.
1	2358	26.77	14.38	0.09	0.40	0.77	0.99	6.78	3.36	0.4476	17.85	11.09	130–85	48%	Normal control.
2	2319	29.43	15.63	0.15	0.34	0.57	0.65	5.42	6.67	0.4435	24.68	15.45	240–160	47%	
3	2357	35.70	18.49	0.10	0.67	0.67	0.95	8.44	6.38	0.4391	27.35	18.50	210–108	52%	Chronic myocarditis.
4	2348	43.48	23.57	0.12	0.40	0.59	1.19	6.52	11.09	0.4707	35.70	21.25	185–95	52%	
5	1992	55.30	38.98	0.14	0.67	3.07	4.27	.....	.....	0.5153	.....	.....	260–110	12%	
6	1954	57.60	36.85	0.15	0.64	0.82	5.70	.....	.....	0.4296	.....	.....	235–115	21%	
7A	2006	95.27	66.66	0.15	0.64	3.68	2.89	.....	.....	0.5363	.....	.....	190–98	Unreadable trace	
7B	2006	90.90	62.50	0.19	0.53	5.08	2.32	6.42	13.86	0.5682	66.66	60.24	190–100	Unreadable trace	
8	2259	128.00	95.10	0.16	0.68	5.29	7.08	5.89	13.80	0.3429	128.00	95.21	130–80	.....	Mercury poisoning.
9	2174	138.10	79.76	0.24	1.67	4.09	4.37	16.32	31.65	0.4216	142.96	85.88	185–140	Unreadable trace[s]	

7A on December 12. 7B on December 17.

CHART XIV.—TABLES SHOWING DETERMINATIONS OF NITROGENOUS BODIES IN BLOOD AND SPINAL FLUID IN CASES OF CHRONIC NEPHRITIS HAVING ONLY VASCULAR CHANGES IN THE EYE-GROUNDS

10	2132	47.51	29.58	0.18	0.40	2.02	3.58	10.23	1.52	0.4500	.....	.....	265–140	33%	
11	2202	71.43	43.07	0.11	0.66	1.71	2.10	6.50	17.28	0.5362	47.62	40.32	245–150	18%	17 cells in spinal fluid
12	2316	95.23	60.00	0.16	0.43	3.68	4.34	8.05	18.57	0.4649	80.00	60.16	213 124	Unreadable trace	

CHART XV.—TABLES SHOWING DETERMINATIONS OF NITROGENOUS BODIES IN BLOOD AND SPINAL FLUID IN CASES OF CHRONIC NEPHRITIS WITH MARKED ALBUMINURIC RETINITIS

13	2354	23.81	14.60	0.10	0.35	0.61	0.99	4.02	3.14	0.4243	20.00	12.50	285–160	28%	Apoplexy.
14	2074	40.98	27.00	0.17	0.39	1.67	2.21	5.22	4.32	0.4400	33.28	26.32	180–130	19%	
15A	2043	54.05	32.14	0.12	0.46	2.74	2.74	.....	.....	0.4558	43.46	26.59	250–166	10%	
15B	2043	60.61	41.54	0.12	1.26	2.30	3.12	10.64	1.63	0.4735	46.58	31.25	250–160	10%	
16A	2108	55.55	29.35	0.09	0.60	2.63	1.59	9.44	11.85	0.4407	37.21	27.77	190–150	15%	4 cells per cm. in spinal fluid.
16B	2108	47.54	25.50	0.15	0.98	2.45	3.66	6.56	8.24	0.3997	33.33	26.00	150–130	11%	Herpes zoster complicating uremia. 91 cells per cm. in spinal fluid.
17A	1882	192.30	113.80	0.20	0.62	8.01	14.39	.....	.....	0.4788	125.00	111.11	248–128	Unreadable trace	16 cells per cm. in spinal fluid.
17B	1882	266.66	166.45	0.21	2.78	7.85	7.66	.....	.....	0.5141	188.69	166.66	250–130	Unreadable trace	Uremia. 23 cells per cm. in spinal fluid.
18	1975	257.70	181.80	0.33	1.51	6.01	30.93	.....	.....	0.4752	.....	.....	208–152	Unreadable trace	Uremia.

15A on December 19. 15B on December 30. 16A on January 4. 16B on January 19. 17A on November 30. 17B on December 14.

[s] Phthalein estimation made three weeks previously at Massachusetts General Hospital.

of the pancreas; pleurisy with effusion long after the pleural fluid had been removed mechanically; tabes in a patient requiring catheterization; meningitis; pernicious anemia following transfusion, migraine, etc.

In the records of successive patients as used above are included many records of individuals who were in the hospital for short periods of time in which only relatively few observations of fluid output were made; so our figures based on these 600 successive patients very likely give an incorrect idea of the frequency of diuresis, indicating that it is less common in the average hospital patient than is really the case. To avoid any error incident to very brief stay under observation, another series of successive records were gone over and all charts of patients who remained in the hospital not less than seven completed days were examined.

A series of 117 such were studied. Of these 69, or 59 per cent., on at least one day showed an output of urine in excess of 1600 c.c., or in excess of fluid intake; while 48, or 41 per cent., did not. In making this division the first day in the hospital is not included, as it often represents an incompleted twenty-four hours. Furthermore, the urinary excretion of the first day frequently is influenced by the excitement of admission to the hospital and by other extraneous factors. It is to be remembered in this connection that we have defined diuresis in a very limited way. In the figures just given numerous factors enter to make the number showing diuresis relatively large. For example, in twenty cases of this group on only one day did the urine exceed, and then but slightly, the fluid intake. This happened on days when for some reason or other the patient drank relatively little fluid, but the total urine on these days when it had exceeded the fluid intake was well below 1600 c.c. in amount. We think that these cases justly may be excluded from the group regarded as showing a diuresis. If this is done the number showing a diuresis represents 41 per cent. of the total. In a number of other cases urinary output was only once slightly above 1600 c.c., or in a long stay in the hospital only occasionally did the urine exceed the fluid intake. Going over the cases in this way there was a definite diuresis in relatively few of the cases, naturally slightly more than in the group in which were included cases in the hospital for only a short stay, but still proportionately a small number.

The analysis of the 600 successive cases given above indicated that chronic cardiac involvement, chronic nephritis, typhoid, and diabetes most often were the conditions in which diuresis occurred. The same conditions were found most commonly as the diagnosis in the patients of this second group showing diuresis. An examination of another group of 100 records in a way similar to the second series gave very similar figures.

The striking things in going over these cases have been the relative infrequency of diuresis even of only short duration in our hospital patients, and the lack aside from digitalis or large fluid intake of an easily assignable cause for such diuresis as occurred. It seemed that possibly a study of a group of cases of nephritis with relation to diuresis might throw some light on the question, inasmuch as this was the only group aside from cases of cardiac insufficiency in which diuresis occurred with any frequency. Consequently, 100 consecutive cases with chronic nephritis who had remained in the hospital not less than one week were examined.

Of these 100 cases of chronic nephritis, 51 showed no diuresis in the sense described above, while 49 had diuresis on at least 1 day. Almost all of the cases of chronic nephritis had hypertension, and 47 of them showed evidence of cardiac lesion diagnosed either as chronic myocarditis or chronic valvular lesion of some kind. This diagnosis of cardiac lesion was based on either definite evidence of cardiac decompensation or on electrocardiographic evidence of disturbance in myocardial function. Of the 100 cases of chronic nephritis, 43 received no diuretic therapy (increased fluid intake, digitalis, theocin, or similar drugs), and of these 12 showed a diuresis while 31 did not; 29 patients received digitalis; 17 with an ensuing diuresis, 12 without diuresis. Of the 17 cases in whom digitalis produced a diuresis, 14 showed very definite evidence of cardiac lesion, while in 2 cardiac decompensation was very probably present as they were cases with hypertension with signs of edema at the bases of the lungs as well as subcutaneous edema. In the one remaining case of this group there was a normal blood-pressure and no signs of cardiac lesion and no physical findings to suggest cardiac decompensation. In 8 patients a large fluid intake resulting from thirst caused diuresis. In three patients given sodium bicarbonate it appeared to cause

diuresis. In 4 patients on a standard nephritic diet, diuresis occurred when either 10 grams of sodium chloride or 20 grams of urea were added to the diet. Particularly interesting are 10 cases in which such diuretic drugs as theobromin sodium salicylate, potassium citrate, caffein, and theocin produced no diuresis.

Curiously enough, in the 100 cases of chronic nephritis these so-called diuretic drugs failed very generally to produce diuresis when used alone. Occasionally when they had been used in conjunction with digitalis there was a diuresis, and here the digitalis alone may have been the cause of the diuresis. The number of cases is, of course, too small to justify the conclusion that this group do not act as diuretics in the condition of chronic nephritis, but these findings justify further our feeling of skepticism, and we hope that they will stimulate renewed study of the problem of the action of diuretics.

Most of the patients in this group had slight if any edema. Possibly this is the cause of so many failures to obtain diuresis in cases without cardiac failure. If so, then diuretic drugs would seem to have little value as eliminants of toxic substances in chronic nephritis without edema. Further evidence certainly is needed on this point to justify the use of diuretics in uremic conditions without edema in view of the evidence which has been accumulated that the diseased kidney is abnormally sensitive to fatigue and that diuretics may cause fatigue and consequent decrease in renal excretion, while in animals with acute lesions they are often demonstrably harmful. However, diuretic drugs do not have even any very constant effect in cases of nephritis with edema and without cardiac decompensation, as is shown by the following cases:

A boy, aged nineteen years (Peter Bent Brigham Hospital, Medical, No. 1225, Chart XVI and XVII), came into the hospital complaining that for about a week he had had edema of his legs, abdomen, back, and cheeks. When he came in his blood-pressure was 160 mm. of mercury. There was evidence of a moderate amount of fluid in his abdomen and in his thorax, and there was the edema of the subcutaneous tissue of which he complained. There was a slight degree of exudation in the retina of one eye. His urine contained a large amount of albumin, many cellular and granular casts, and a few red-blood cells. His phenolsulphonephthalein excretion in two hours was 34 per cent. His total non-protein nitrogen was

35 mgm. per 100 c.c. of blood. He came into the hospital on May 20 and remained until September 9. During this time his phenolsulphonephthalein excretion fluctuated between the figure given above and a minumum figure

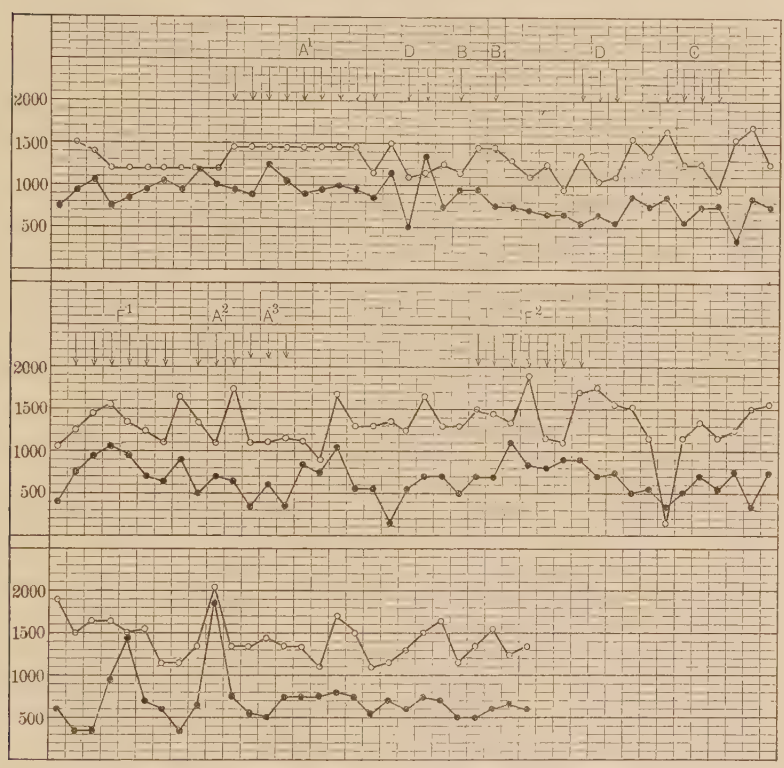

CHART XVI.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under A^1 indicates a day on which the patient received three doses of 0.1 gm. each of powdered digitalis leaves; under A^2 a day on which the patient received two doses of the same, and under A^3 a day on which the patient received two doses of 0.05 gm. each of powdered digitalis leaves. Each arrow under B indicates a dose of 0.5 gm. of theocin; under C a day on which the patient received 0.13 gm. of caffein citrate every four hours; under D a dose of 0.5 gm. of theobromin sodium salicylate; under F^1 a dose of 1 gm. of potassium citrate, and under F^2 a day on which the patient received two doses of 0.5 gm. each of potassium citrate.

of 15 per cent. in two hours; whereas his blood nitrogen fluctuated between 35 mgm. and 44 mgm. per 100 c.c. of blood, with one reading of 71 mgm. per 100 c.c. of blood at a time when there was no other evidence of increased renal insufficiency. During his stay in the hospital the amount of albumin

in his urine gradually decreased in amount, and the edema in various parts of his body all disappeared. As shown by the appended chart (Chart XVI), theocin, theobromin sodium salicylate, caffein citrate, potassium citrate, and digitalis all failed to produce any diuresis, as shown by the twenty-four-hour amount of urine in relation to the fluid intake. It was thought possible that in this case the drugs might have produced an immediate

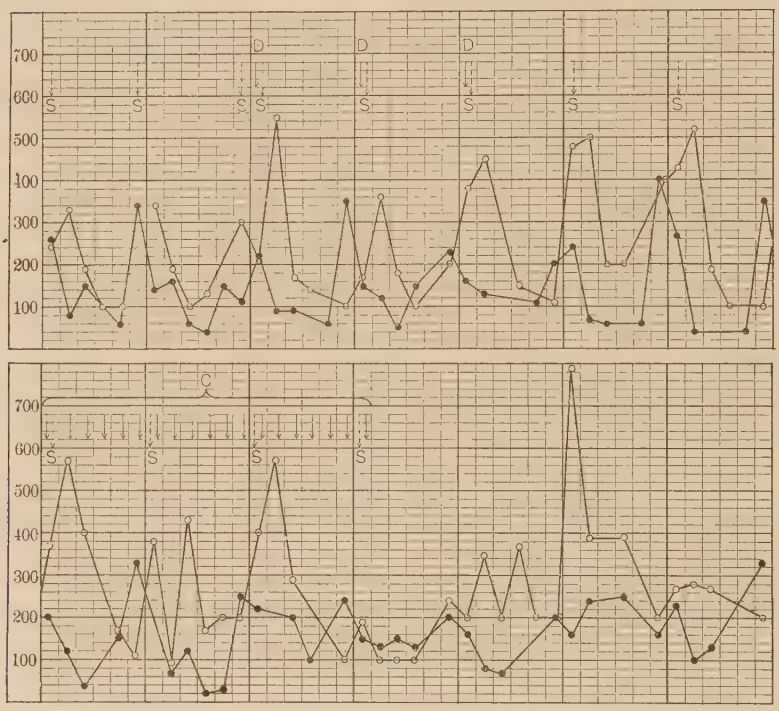

CHART XVII.—The solid black dots indicate the four-hour amount of urine in cubic centimeters. The black circles indicate the four-hour amount of fluid intake in cubic centimeters. Each arrow under C indicates one dose of 0.13 gm. of caffein citrate, and under D indicates a dose of 0.5 gm. of theobromin sodium salicylate. Each arrow over S indicates an electric light sweat bath in bed.

diuresis which was offset by subsequent fall in excretion. To see whether or not this was the case for a considerable period of time, the patient's urine was collected in four-hour periods for fourteen days, but as shown by the chart (Chart XVII) there was no evidence of diuresis of this type.

In another patient, aged thirty-eight years (Peter Bent Brigham Hospital, Medical, No. 1754, Chart XVIII), single doses of theocin seemed to produce no effect. This patient came into the hospital on October 11 and remained

until November 15. He noticed eleven days before coming in that his legs began to swell, and five days before he came in that his face was swollen; two days before he came in the edema had involved his genitalia. This patient had a normal blood-pressure, signs of fluid in his thorax, possibly some fluid in his abdomen, and a marked degree of subcutaneous edema. When he came in his urine contained a large amount of albumin, many hyalin and granular casts, many of which had fat attached, but very few red-blood cells. His excretion of phenolsulphonephthalein was 28 per cent. in two hours. His non-protein nitrogen was 36 mgm. per 100 c.c. of blood. During his stay in the hospital his blood nitrogen decreased to 24 mgm. per 100 c.c. of blood, and his phenolsulphonephthalein excretion increased to 39 per cent. The albumin in his urine decreased in amount

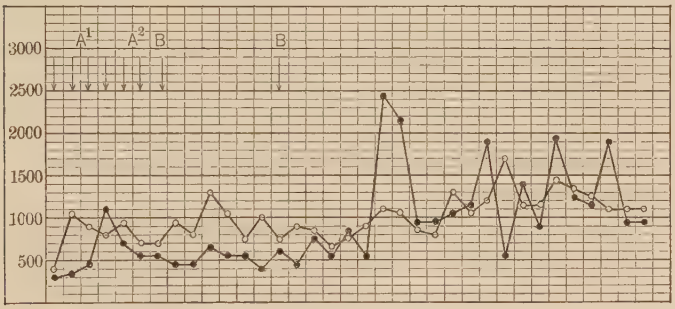

CHART XVIII.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under A^1 indicates a day on which the patient received three doses of 0.1 gm. each of powdered digitalis leaves; under A^2 a day on which the patient received two doses of 0.05 gm. each of powdered digitalis leaves. Each arrow under B indicates a dose of 0.3 gm. of theocin.

and the casts decreased in numbers. Chart XVIII shows the lack of effect of the theocin and a subsequent diuresis on two days for which no cause could be assigned.

Another patient of similar type, aged thirty-one years (Peter Bent Brigham Hospital, Medical, No. 1624, Chart XIX), was in the hospital from September 10 to November 18. Swelling of his legs developed about three and a half months before he came in. When he came to the hospital he showed considerable edema of his legs and trunk, with definite signs of fluid in his abdomen. His phenolsulphonephthalein excretion varied between 28 per cent. and 52 per cent. in two hours. His non-protein nitrogen was 23 mgm. per 100 c.c. of blood. His urine picture was essentially the same as in the preceding patient. His blood-pressure was 150 mm. of mercury. In this patient, as shown by the chart (Chart XIX), theobromin

sodium salicylate and theocin each appeared to produce a slight though not constant diuresis.

A fourth patient, aged thirty-five years (Peter Bent Brigham Hospital Medical, No. 1879, Chart XX), was in the hospital from November 7 to December 12 with a history that three days before entrance his feet had begun to swell and he had some dyspnea. This was preceded about a week and a half before by nausea, with some vomiting. When he came into the hospital he had marked edema of his feet and lower legs with many coarse rales in his lungs. His blood-pressure varied between 140 and 190 mm. of mercury. His phenolsulphonephthalein output varied between 30 per cent. and 46 per cent. in two hours, and his blood nitrogen between 50 and 82.5 mgm. per 100 c.c. of blood. His urine showed a large trace of albumin, hyalin, and finely and coarsely granular casts.

On a diet of 800 c.c. of milk and no added fluid he had a moderate diuresis (Chart XX). He was then put on theocin, 0.3 gm. twice a day, from November 18 to 22, during which period his diuresis was rather less than it had been previously. His edema had to a considerable extent disappeared. After theocin was stopped there was a slight temporary diuresis. Then on a larger intake of fluid slight edema developed. With a reduction in the fluid and the patient back in bed there was quite definite diuresis, as shown by the chart, though he received no drug treatment.

A fifth patient, aged forty-five years (Peter Bent Brigham Hospital, Medical, No. 1885, Chart XXI), was in the hospital from November 9 to December 9, with a story that seven months before admission he had had pneumonia, and this had been accompanied by edema of his lower extremities, which a little later increased so that it involved his genitalia, and his abdomen began to swell. In another hospital this edema disappeared, but returned about four months ago shortly after discharge from that hospital. It remained small in amount, however, until about two weeks before admission to the Brigham Hospital, when it markedly increased. He also began to have nausea and vomiting. When he came into the hospital he had signs of ascites, edema of the legs, scrotum, and abdominal wall. His heart showed the physical signs of aortic and mitral insufficiency. His blood-pressure varied between 150 and 210 mm. of mercury. His phenolsulphonephthalein output varied between 22 per cent. and 33 per cent. in two hours, and his blood nitrogen between 37.5 and 39 mgm. per 100 c.c. of blood. His urine showed essentially the same picture as the preceding case.

When he first came into the hospital he was put on a diet of 800 c.c. of milk, with no added fluids. On November 15 he was put on a salt-free diet. On November 17 he was given 0.3 gm. of theocin twice, and on November 18 and November 19 he was given the same amount of theocin at 8 P.M. without any diuresis (Chart XXI). On November 22, 3700 c.c.

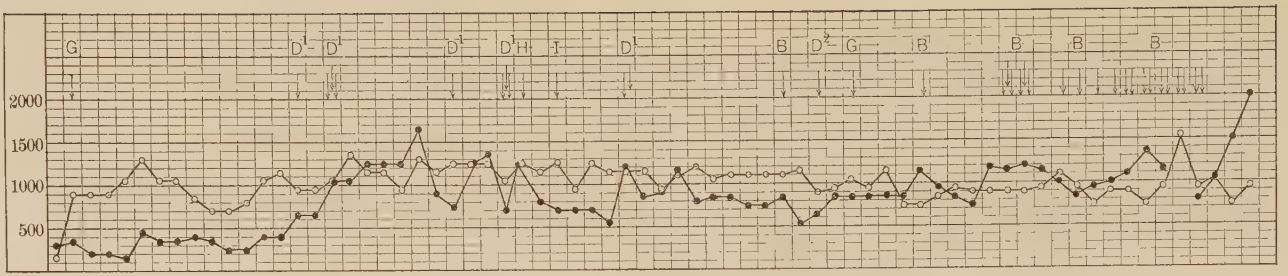

CHART XIX.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under B indicates a dose of 0.3 gm. of theocin; under D^1 a dose of 0.25 gm. of theobromin sodium salicylate; under D^2 a dose of 0.5 gm. of theobromin sodium salicylate; under G removing 2650 c.c. of ascitic fluid; under H 20 gm. of urea, and under I, 10 gm. of sodium chloride.

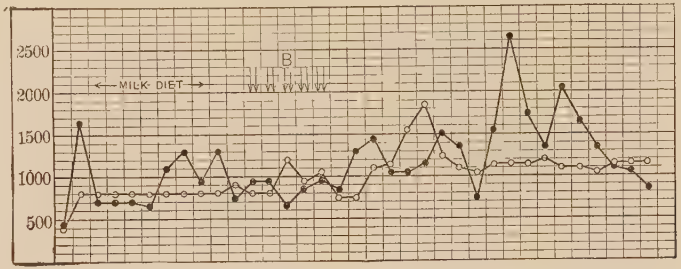

CHART XX.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under B indicates a dose of 0.3 gm. of theocin.

of fluid were removed from his abdomen. Finally, on November 27, he was put on small doses of digitalis, twice a day, with a definite diuresis.

That diuretic drugs are not always ineffectual is well shown by a cardiac case with aortic stenosis and insufficiency who was in the hospital from January 23 to March 21 (Peter Bent Brigham Hospital, Medical No. 2212, Charts XXII and XXIII) with marked edema. As shown by the chart (Chart XXII), theocin in connection with digitalis produced a marked diuresis, though theobromin sodium salicylate did not have the same result. With the theocin,

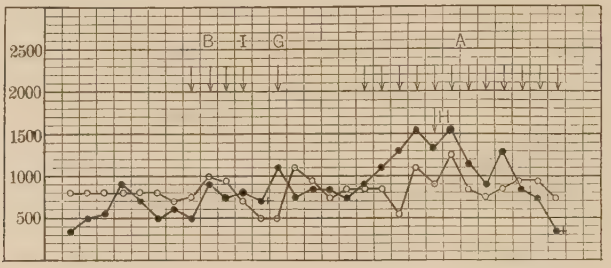

CHART XXI.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under A indicates a day on which the patient received two doses of 0.05 gm. of powdered digitalis leaves; under B a dose of 0.3 gm. of theocin; under G a day on which 3700 c.c. of ascitic fluid was removed; under H, 20 gm. of urea and under I, 10 gm. of sodium chloride.

however, he became markedly nauseated. It was thought that this difference in action might be due to differences in absorption of the two drugs. To determine this they were given intravenously at a later period during a second stay in the hospital and in the same relation to digitalis. The same difference in action was apparent after intravenous dosage; theocin produced a striking diuresis, as shown by the chart (Chart XXIII), while theobromin sodium salicylate produced a very slight increase in urine output. Interestingly, nausea again occurred, though to a less extent, than when the drugs were given by mouth.

These several results seem to justify our skepticism in regard to the use of diuretics. Certainly more information is needed before we can employ diuretics efficiently in cases of renal or cardio-renal disease.

D. Functional Tests in Relation to Anatomical Changes in the Kidney. Up to the present time 18 cases of chronic nephritis

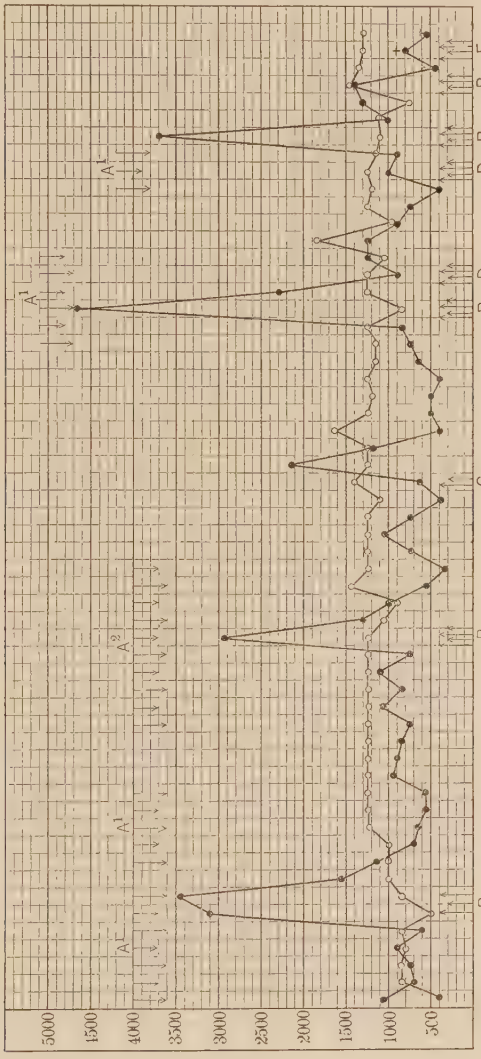

Chart XXII.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under A^1 indicates a day on which the patient received three doses of 10 c.c. each of an infusion of digitalis. Each arrow under A^2 indicates a day on which the patient received two doses of 10 c.c. each of an infusion of digitalis. Each arrow over B indicates one dose of 0.5 gm. of theocin. Each arrow over C indicates one dose of 0.2 gm. of caffein sodium benzoate. Each arrow over D indicates one dose of 0.3 gm. of theobromin sodium salicylate. Each arrow over E indicates one dose of 0.5 gm. of theocin sodium acetate.

have come to autopsy at the Brigham Hospital upon which enough clinical work had been done to make a comparison between the clinical and anatomical findings of interest. Most of these cases

were seriously ill when they were admitted to the hospital, and consequently could not be put upon standard diets to which were added salt and urea to determine the relative ability of the kidney to excrete salt and nitrogen. Determinations of phenolsulphonephthalein excretion and estimations of the non-protein nitrogen in the blood were made, and, in addition, careful general clinical examinations were carried out.

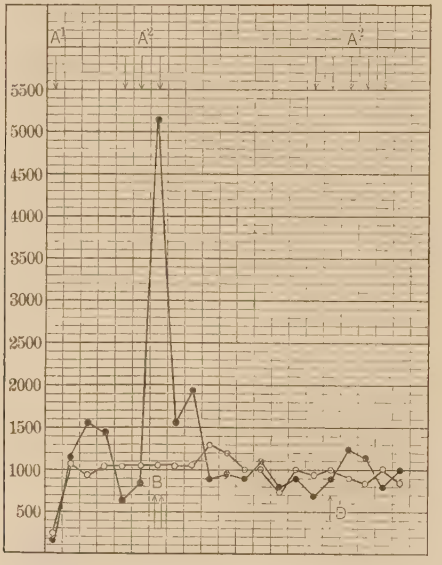

CHART XXIII.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. The arrow under A^1 indicates a subcutaneous dose of 1 c.c. of digipuratum and under A^2 a day on which the patient received three doses of 10 c.c. each of an infusion of digitalis. The arrows at B indicate two doses of 0.5 gm. each of theocin given intravenously and at D a dose of 1 gm. of theobromin sodium salicylate given intravenously.

In the 18 cases, microscopic study of the kidney showed a chronic vascular nephritis, in the sense used by Mallory in his recent book, in 14 cases, and in 4 cases the lesion was a chronic glomerular nephritis. The study of blood nitrogen, phenolsulphonephthalein excretion, and the excretion in the urine of albumin and casts did not give results during life which justified a definite diagnosis in the anatomical sense on many of these cases. In other words, during life

it was not possible to accurately foretell what histological changes would be found in the kidneys in those patients who were studied in the last stages of a chronic nephritis. The clinical study of those cases has given much evidence of use in regard to prognosis. In a functional sense it has been possible to classify the cases into various groups, but it has not been possible to diagnose accurately the anatomical condition of the kidney. As has already been said, test renal meals and test diets could not be applied in these cases. Whether a more satisfactory anatomical diagnosis could have been made if these had been carried out is merely a matter of speculation.

It is hoped that as time goes on cases which we have studied in the earlier stages will return to the hospital for repeated examinations as their disease progresses, and in the last stages may be under observation. If autopsies can be obtained when such patients die, an opportunity will be afforded to compare the results of functional studies with end anatomical conditions. It is only in the earlier stages of the nephritis that satisfactory dietary studies can be made as well as other methods of estimating renal function. Until this happens it will not be possible to say how far an accurate anatomical diagnosis can be made during life. We feel sure that such functional studies as can be made in the late stages of chronic nephritis do not make possible an accurate anatomical diagnosis, because at this stage almost all parts of the renal function are at a low level of efficiency.

CONCLUSIONS

A. Test Renal Meals in Relation to Renal Function.

1. Of two general methods used the v. Monakow standard diet with days of added salt or urea and the Hedinger and Schlayer test day on a mixed diet, the first requires about ten days of hospital study and the second three days. Using the two methods on a series of patients we have obtained very similar results by each.

2. Though similar the results are not quantitatively identical. The same is true for the same test repeated several times on the same patient.

3. For the Hedinger and Schlayer test there is no constant normal curve of excretion. Normality consists in the ability to vary from period to period the amounts and concentration of the substances quantitated. Abnormality consists in a more or less marked degree of fixation in all of these values from period to period.

4. Fixation in excretion of nitrogen seems to develop at a later period in most cases than is true for water and salt.

B. Quantitative Studies of Non-protein Nitrogenous Bodies of the Blood. 1. Urea nitrogen in a series of cases averaged 63.4 per cent. of the total non-protein nitrogen of the blood, and its increase was usually proportionate to the increase of the total non-protein nitrogen.

2. Ammonia nitrogen increased slightly but not proportionately. The same held for uric acid and amino-acid nitrogen.

3. Creatinin showed roughly a proportionate increase.

4. The difference between determined forms of nitrogen and total non-protein nitrogen was greatest in cases with clinically most severe symptoms.

5. In the spinal fluid the increase in nitrogen is almost solely in urea nitrogen except in cases of anuria.

6. We can see no advantage in quantitating the nitrogen of the spinal fluid over quantitating it in the blood.

7. No relationship existed between the amount of non-protein nitrogen in the blood and changes in the retina.

C. Diuresis in Relation to Diuretics. 1. Diuresis is relatively infrequent in the average hospital patient.

2. Except for diuresis in cardiac cases following digitalis, diuresis bears an inconstant relation to diuretic drugs.

3. In cases of nephritis with or without edema and without cardiac decompensation, diuretic drugs more often fail to produce a diuresis than the reverse.

4. In cardiorenal cases, diuretic drugs often produce a striking diuresis.

5. Our observations justify a healthy skepticism as to the efficacy of diuretic drugs in cases of nephritis without cardiac decompensation.

D. Functional Tests in Relation to Anatomical Changes in the Kidney. 1. In 18 cases of chronic nephritis dying and coming to autopsy no constant relations have been found between anatomical lesions and renal function insofar as excretion of phenolsulphonephthalein, albumin in the urine, casts, presence or absence of edema, blood-pressure determinations, etc., are concerned.

POISONING BY BICHLORIDE OF MERCURY AND ITS TREATMENT

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The recent increase in the number of cases of poisoning by bichloride of mercury is largely due to the newspaper notoriety which was given to a case of accidental poisoning occurring about four years ago. The public were instructed in all the details of the symptoms, and great stress was laid not only upon the sureness of the fatal ending, but also upon the painlessness and lack of suffering which accompanied the illness of that particular victim. The repetition of similar publications and the ease with which the drug could be obtained appealed to would-be suicides, and now both intentional and accidental cases of poisoning have become a common occurrence in hospital practice. Bichloride of mercury tablets have been used for some years as a household article to treat the ordinary slight wound infections of the family, to rid the house of bed vermin, and in many cases as a preventive of conception.

The commonest accident resulting in poisoning is the swallowing of the tablets in mistake for some headache remedy: such accidental cases about equal in number those of attempted suicide. In New York City the cases of suicide by poisoning due to the principal drugs for the past twenty-five years are shown in the following table, arranged in five-year periods:

	1890 1894	1895 1899	1900 1904	1905 1909	1910 1914
Paris green and arsenic	155	170	99	47	48
Carbolic acid	73	627	1455	325	154
Opium and morphin	42	56	56	48	29
Bichloride of mercury	4	10	9	28	104
Illuminating gas	65	315	628	1149	1554
Other poisons	58	94	104	196	237
Total all poisons	397	1272	2351	1793	2126

Figures from 1890 to 1897 inclusive represent former city of New York.
Figures from 1898 to 1914 inclusive represent greater New York.

This table shows there is a fashion in the methods of suicides, and that poisoning by arsenic and Paris green and by carbolic acid are on the decrease, that by opium is stationary, while poisoning by illuminating gas and bichloride of mercury are becoming popular methods, and are on the increase. Of the 155 cases of suicide by bichloride recorded in the past twenty-five years, 73, or nearly half of them, have occurred in the last two years. This question, therefore, forms an important social problem. The regulation of the sale of the poison in the form of antiseptic tablets of corrosive sublimate is already begun and should be undertaken and enforced by all boards of health.

The symptoms of poisoning by the bichloride came into prominence and were studied first as a complication of surgical operations and in obstetric practice. In the cases of wound absorption the initial toxic gastritis is absent and the kidney symptoms and salivation are less prominent than the colitis. The absorption of the drug is gradual in these cases, and its effect is shown in great part in the efforts of the large intestine to eliminate it, with the result of an intensive and often fatal ulcerative colitis. A case of bichloride poisoning resulting from the surgical accident of delivering about 1.5 grains of the salt into the vein of a patient during a postoperative saline infusion gave the following sequence of events, and throws much light on the symptomatology of the condition. The symptoms in this case are not the same as result from absorption from surgical wounds, but resemble the cases of poisoning with a predominance of kidney and intestinal symptoms. The infusion was given on the fifth day after a laparotomy. Prior to the giving of the drug the

patient had passed about 30 ounces of urine a day and had had a daily evacuation of the bowels as the result of enema or saline catharsis. There was no previous vomiting and the pulse ranged from 80 to 90. The wound was slightly infected and the temperature ranged from 100° to 101.8°. The infusion was given because of postoperative sepsis of mild type. Eight hours after the infusion the patient vomited and the pulse became irregular and weak. The vomiting was repeated several times during the first twenty-four hours. The secretion of urine was interfered with from the start and about 2 ounces were secreted during this period. During the second twenty-four hours 2.5 drams of urine were obtained by catheter and the bowels began to move involuntarily and continuously. The pulse was irregular and weak, the rate about 120, and the breathing was labored. The involuntary stools continued and became bloody and full of mucus. Nine drams of urine were drawn by catheter during the day. The following thirty-six hours presented the same symptoms of a severe colitis and an almost total suppression of urine, and the patient died in extreme exhaustion five and a half days after the infusion without improvement in the colitis or the urinary symptoms. There was marked mental distress, but none of the ordinary symptoms of uremia.

An autopsy was held and the true etiology discovered by the microscopic appearances of the kidneys. The essential findings were as follows: The heart was normal; the lungs showed some congestion and edema of the lower lobes. There were large masses of clotted blood in the gastrohepatic ligament, the gastrocolic and the gastrosplenic ligaments, and in the lesser peritoneal cavity. The gall-bladder had been removed at the laparotomy. The liver was very friable and deeply bile-stained. The bile ducts were much thickened and dilated and contained many small black calculi. In the common duct there was a stone about 6 mm. in diameter. The spleen showed nothing special. The kidneys were very large and deeply jaundiced; there were several cysts on the surface. The capsule stripped with some difficulty, leaving the surface roughish. On section the kidneys were very edematous and showed evidence of acute degeneration; the color was pale yellow, with small hemorrhagic spots. The mucous membrane of the stomach

was much swollen, red, and covered with a layer of thick mucus. The intestines were filled with blackish, watery feces, mixed with a large amount of mucus. The descending portion of the colon and sigmoid were covered with membrane and deeply congested. The lesion was most severe in the sigmoid. The glands were normal. The anatomical diagnosis was: Hemorrhage into the lesser peritoneal sac and gastric ligaments, chronic diffuse nephritis with acute degeneration, general jaundice, biliary calculi in bile ducts.

The microscopic examination of the organs showed biliary pigmentation in the liver cells and bile capillaries, also in the kidney cells. The kidneys showed an extensive parenchymatous degeneration and calcification of the walls of the convoluted tubules, with large casts which were still present in the tubules. There was a small amount of connective tissue between the tubules. The glomeruli showed no important lesions. These changes in the kidney are those characteristic of poisoning by bichloride of mercury.

In the cases of poisoning caused by swallowing the drug the symptoms begin promptly after it is taken. Abdominal distress and pain at first in the epigastrium and later more general, are the primary symptoms. Nausea and vomiting of the stomach contents and later of mucus which is more or less blood-stained, accompany the pains. This gastritis is usually promptly treated with egg albumen or milk and lavage and yields quite readily to such treatment, so that the patient is comparatively comfortable after thirty-six hours rest and abstinence from food. The mouth shows signs of a mercurial stomatitis in about twenty-four hours, but this rarely is as severe as usually accompanies salivation from calomel. If the poisoning is left to run its course uninfluenced the patient's attention is called to the diminishing amounts of urine in from forty-eight to seventy-two hours after taking the drug. This may develop to a complete anuria and the patient dies without restoration of the secreting power of the kidneys. When this occurs the patient may remain free from cerebral symptoms for the better part of a week until a terminal form of low delirium supervenes and a weakening heart action proves fatal. There are none of the regular evidences of uremia and convulsive seizures do not occur.

If the kidney condition is survived and its function reëstablished, and in those cases which do not develop this extreme degree of nephritis, there is apt to be a membranous colitis with deep ulcerations and hemorrhages which may develop and prove fatal even after several weeks have elapsed from the time of the original poisoning.

In a case recently observed by one of us in consultation outside the hospital, a patient, who denied having taken the drug, had been anuric for three days. Calculus anuria was suspected, but an examination by *x*-ray showed no stone, and examination of a stool revealed the presence of mercury. Free colonic irrigations were begun and after five days of anuria the patient passed 1 dram, on the following day 5 drams, and then the daily amount slowly rose until after about a week or ten days of reëstablished urination he was passing over 50 ounces of urine. Notwithstanding this, at about the end of three weeks he developed a severe colitis, with the passage of large casts of the colon, and died after a large intestinal hemorrhage.

The therapeutics of corrosive-sublimate poisoning up to the present have been quite unsatisfactory. The cases have regularly developed anuria on or about the fourth day after taking the poison, and progressed to subsequent death, from lesions of the liver and colon, with or without the reëstablishment of the urinary secretion.

Radical procedures have been tried in such cases, including the surgical manipulations of loosening the kidney capsule, but it may well be doubted if such operative treatment has had any specific influence on the course of the clinical picture. The following treatment has been gradually formulated as the result of caring for ten consecutive cases of varying severity which have all resulted in a cure. The first two cases of poisoning resulted from the insertion of two tablets (15 grains) into the vagina, and were treated by favoring the elimination of the poison by frequent and prolonged colonic irrigations with normal saline and by such local measures as were needed to allay the severe vaginitis.

The remaining cases were due to swallowing one or more of the commonly used tablets contining 7.5 grains of corrosive sublimate.

The treatment in the detail now used at St. Luke's Hospital as a routine has been elaborated through the help of the method of Vogel,[1] by which mercury is readily detected in stomach contents, urine, and stools. By this procedure one can determine not only the diagnosis and the necessity of beginning treatment, but also, in some cases, the length of time treatment should be continued. A certain number of cases are brought to institutions either pretending to have taken bichloride, or fearing that they have taken it by mistake in the dark, etc. It is particularly important to know if a patient has not taken the poison, for the treatment is most irksome to the patient and entails unusual activity on the part of the nursing department.

Vogel's method consists of separating the mercury from its albuminous combinations in the organic material to be examined and then subliming it in a sealed tube to form an amalgam on a small piece of dentist's gold. Vogel states that "if mercury is present it will manifest itself by the appearance of a silvery patch of amalgam on the gold foil. If the amount of the metal is exceedingly minute there will be simply a pale discoloration of the gold, seen to better advantage with the hand-lens or by removing the pellet from the tube and examining it with the low power of the microscope, but if the amount is larger the deposit on the gold will be very easy to recognize."

Before outlining the treatment, attention is directed to some characteristics of these cases which have been treated and studied by Vogel's method of detecting mercury in excreta. In the first place it has been found that mercury in cases of bichloride poisoning is regularly found in the stomach for several days after the ingestion of the poison. That it is not wholly swallowed in the saliva but is secreted by the stomach in an effort to eliminate it from the body, and that it is not part of the poison held in combination with the mucous membrane of the stomach, seem to be indicated by the fact that after several days the tests are negative, to become positive again before all the mercury is eliminated. This corresponds to the behavior of the tests conducted upon urine and feces, late

[1] Jour. Amer. Med. Assn., 1914, lxii, 532.

in the poisoning. Certain experiments are given below which indicate the same thing.

Another feature that is a determining factor in the length of time treatment should be carried on, is the behavior of the mercury elimination after the patients, apparently, are entirely recovered. A reference to the tests for mercury under the case histories will show the very long time it takes to free the system of mercury after bichloride poisoning. In Case VI, where nephritis preëxisted before the poisoning, in Case VII, where successive doses were taken, and in Case VIII, where a large dose was taken, the excretion of mercury by the kidneys, the colon and the stomach, lasted for days after all symptoms had cleared up. It has become quite apparent that treatment need not be kept up after the urine, and particularly the stools begin to show negative results.

Treatment. The treatment as it is formulated at present for cases coming under observation early is as follows: The first indication is to give the patient the whites of several eggs and then to wash out the stomach thoroughly. This has usually been done before the patients are admitted to the hospital. On admission the stomach contents are expressed and examined for mercury, the stomach is thoroughly washed, and a pint of milk introduced. If no stomach contents are obtained before lavage, then the lavage water is examined for mercury. Urine passed spontaneously, or that obtained by catheter, is examined for mercury. The metal appears in the urine in from three to twenty-four hours after swallowing it. If more than a day has elapsed since the poisoning occurred, a stool should also be examined for the poison. If the first lavage does not allay the nausea and vomiting it is repeated after an hour and the following routine is begun as soon as the stomach will permit.

1. The patient is given every other hour 8 ounces of the following mixture: Potassium bitartrate 1 dram, sugar 1 dram, milk sugar $\frac{1}{2}$ ounce, lemon juice 1 ounce, boiled water 16 ounces. Eight ounces of milk are administered every alternate hour.

2. The drop method of rectal irrigation with a solution of potassium acetate, a dram to the pint, is given continuously. The amounts of urine secreted under this treatment are very large, Case

VIII passed 269 ounces in twenty-four hours on the fourteenth day of treatment.

3. The stomach is washed out twice daily.

4. The colon is irrigated twice daily, in order to wash out whatever poison has been eliminated in that way.

5. The patient is given a daily sweat in a hot pack.

It is imperative to emphasize the necessity of keeping up the treatment with the colonic drip enteroclysis day and night without interruption. It entails discomfort for the patient, but the cases of accidental poisoning are always willing to do anything to recover from their plight, and the attempted suicide usually repents rapidly of his error, and the hope of his life being saved stimulates his patience and desire to coöperate.

In cases in which one single dose has been taken, after two negative examinations of the urine, on successive days, it seems legitimate to stop the treatment. In the fifth case, the urine was found to contain no mercury on at least two examinations before discharge. In view of the behavior of subsequent cases, which have been more thoroughly studied it is probable that this patient excreted mercury for some time after leaving the hospital. For the less severe cases, a week may be a sufficient time for treatment. When large or successive doses have been taken, or when there is a preëxisting kidney lesion, or when treatment begins several days after the poison is taken, longer periods of treatment, up to three weeks, are necessary.

It is interesting to consider how much damage the kidney suffers as a result of eliminating, even in a highly diluted form, an amount of mercury, which hitherto in medical experience has led to fatal results. That such damage is not always great, is indicated by the fact that Case V eliminated 76 per cent. of phenolsulphonephthalein in two hours, the second day that his urine was free from mercury. In Case III the phenolsulphonephthalein excretion was 55 per cent. Six weeks after discharge she was apparently free from sequels of her poisoning.

With one exception all these patients came under treatment within twenty-four hours of taking the poison. In cases which have reached the stage of anuria, however, favorable results cannot always

be expected. While it is perfectly possible to reëstablish urination, the cases quite regularly go on to a fatal termination, with degenerative liver changes, and a colitis of the so-called diphtheritic type. In one of the present cases (VI), in which there was preëxisting nephritis, the urinary output was reduced to 32 minims in twenty-four hours on the fifth day after taking the drug, in spite of the fact that treatment was begun three hours after the poisoning. Recovery resulted, but the treatment was much longer than usual. Two of the cases were in the hospital over six weeks and gave positive Wassermann reactions, which were entirely unaffected by the poisoning.

Under the treatment detailed above these cases quiet down to their routine, and, as a rule, do not suffer except from the discomforts of the therapeutic measures. The stomach becomes tolerant of the milk diet and the alkaline drink after twenty-four to thirty-six hours. The kidney secretion at first is excessive and may run up to 130 or more ounces in the twenty-four hours. This usually diminishes in spite of the continued exhibition of fluid between the fifth to the tenth day and may nearly stop altogether as in Case VI. It is at this period that the continuous water cure and the rest in bed must be insisted upon. If this period is successfully passed the secretion of urine again increases often to a higher level than at first. The mercury itself seems to act as a diuretic at this stage of the treatment. The bowels usually show some irritation but when the treatment is faithfully carried out the tendency to diarrhea and colitis is regularly controlled by the colonic irrigations, and other medication for this symptom has been rarely necessary.

In order to clear up some of the toxicological points which have been raised by the study of these cases Professor Lieb has carried out the following experiments in the pharmacology laboratory at the College of Physicians and Surgeons. Several animals were operated on under narcosis and after tying off the esophagus so that no connection was left between the pharynx and the stomach, a hypodermic dose of mercuric bichloride was given. The excretion of the poison was then studied by the Vogel method. Three series of experiments were done. In series I two rabbits were used. After

the above preliminary operation each received 20 mgr. of corrosive sublimate hypodermically. After a few hours mercury was found in the contents of the stomach and in that of the colon of both animals. In series II three decerebrated cats were employed and prepared in the same way as given above. The presence of mercury was demonstrated in two of these animals in the urine and feces and also in the stomachs after from four to eight hours. In series III five decerebrated cats were again experimented on and both the esophagus and the duodenum were tied off. From 15 to 20 mgr. were injected into the jugular vein. Three cats gave a positive reaction after from six to eight hours. Another line of investigation concerning the elimination of mercury was made in the wards. Two patients who needed hot packs were receiving weekly hypodermic doses of the salicylate of mercury. In both cases pads of filter paper were placed upon the skin of the axilla and after being saturated in the sweat of the patients reacted positively to the Vogel test for mercury.

CASE HISTORIES

CASE I.—Admitted December 8. Three days before admission the patient had inserted two 7.5-grain corrosive sublimate tablets in the vagina to relieve pain in the lower abdomen. Soon afterward she began to have severe abdominal pain and her mouth became sore and salivated. She had vomited four times before admission.

Physical Examination. Patient appears ill and uncomfortable; mouth is foul, with sordes on teeth and gums; tongue is badly coated; there is moderate salivation; tonsils and pharynx are congested; the parotid gland on each side is swollen and tender. In the vagina there are yellow and dark brown sloughs on the inner side of each labium major, also yellow and white sloughs on both sides of vagina. The cervix is red and swollen, and there is a watery discharge from the os uteri.

December 9. A saline douche was ordered twice daily; gastric lavage was given, followed by castor oil, through the tube. Colon irrigation (four gallons) was repeated twice daily.

December 23. The patient's condition has decidedly improved in the last few days; the mouth is much cleaner; she still has a vaginal discharge. The patient left the hospital against advice, and was reported well three years later.

Extract from urine chart:

Date.	Amount. c.c.	Reaction.	Specific gravity.	Albumin.	Sugar.	Microscopic.
Dec. 9	720	Acid	...	Trace	0	Many red blood cells.
Dec. 10	840	Acid	...	Trace	0	No blood (catheterized).
Dec. 11	900	Acid	1030	Trace	0	Urates; no casts found.
Dec. 12	540	Acid	...	Trace	0	Pus cloud.
Dec. 13	750	Acid	1036	Trace	0	Pus sediment.
Dec. 14	840					
Dec. 15	540	Acid	1030	Trace	0	Pus cloud.
Dec. 16	420	Acid	1030	Trace	0	Pus and blood sediment.
Dec. 17	660	Acid	...	...	0	Pus and blood sediment.
Dec. 18	540	Acid	1014	Trace	0	Pus cloud.
Dec. 19	420	Alkaline	1035	Trace	0	Pus cloud.
Dec. 20	420	Acid	...	Trace	0	Few leukocytes and epithelial cells.
Dec. 21	960	Alkaline	1026	Faint trace	0	Hyaline casts.

CASE II.—Admitted November 21. On the morning of the day of admission, at 2 A.M., the patient had inserted one 7.5-grain bichloride of mercury tablet in the vagina to avoid conception. Soon afterward she had severe burning sensation in that region and attempted douching, without success. Realizing the gravity of the situation, she came to the hospital, complaining less of pain in the vagina than of peculiar paresthesia and cramp-like pains in the hands and feet. No salivation is evident.

Physical Examination. Negative, except for a good deal of redness of vulva, with seropurulent discharge from vagina. Mucous membrane of vagina is covered with a white slough. Cervix is red. Treatment was ordered as follows: An alkaline douche twice daily, forced fluid diet; a saline colon irrigation twice daily. She was discharged from the hospital at the end of a week.

Extract from urine chart:

Date.	Amount. c.c.	Reaction.	Specific gravity.	Albumin.	Sugar.	Microscopic.
Nov. 21	1620	Acid	1008	Faint trace	0	Many leukocytes; no casts.
Nov. 22	3390	Alkaline	1006	Faint trace	0	Few hyaline casts.
Nov. 23	4320	Alkaline	1008	Faint trace	0	Few hyaline casts.
Nov. 24	3990	Alkaline	1008	Faint trace	0	Few hyaline casts.
Nov. 25	4920	Alkaline	1014	Faint trace	0	Few hyaline casts.

Case III.—Admitted February 12. Twenty-four hours previous she had swallowed three 7.5-grain bichloride of mercury tablets in mistake for soda mints. Immediately she drank milk mixed with eggs, and a doctor arriving a half hour later washed out her stomach. She began to vomit soon after taking the tablets, but this was relieved by the lavage. Six hours before admission she began to have epigastric pain and abdominal cramps, accompanied by diarrhea. Urine is scanty and she has a headache and sore throat.

Physical Examination. Negative except for general abdominal tenderness, which was most intense over lower half.

Treatment. On admission she was put on a continuous rectal irrigation by the drop method, containing potassium acetate, one dram to the pint. This was continued from February 12 to 17; patient then complained of soreness about the rectum and of the proctoclysis making her very nervous. She was then given a colon irrigation each day for four days, when the proctoclysis was again started and continued until discharge. Hot packs were given daily while in the hospital. The lumbar region over the kidneys was cupped every three hours during first three days she was in the hospital.

Patient left the hospital February 28 in very good general condition, and although advised to remain in hospital until the urine was clear of albumin, she left against advice.

Extract from urine chart:

Date.	Amount. c.c.	Reaction.	Specific gravity.	Albumin.	Sugar.	Microscopic.
Feb. 12	180	Acid	1025	Marked trace	0	Few hyaline casts.
Feb. 13	750	Neutral	1022	Marked trace	0	Hyaline and granular casts.
Feb. 14	2450	Alkaline	1019	Marked trace	0	Hyaline and granular casts.
Feb. 15	1500	Alkaline	1013	Marked trace	0	Pus cloud.
Feb. 16	400	Acid	1022	Marked trace	0	Hyaline and granular casts.
Feb. 17	925	Neutral	1021	Faint trace	+	Hyaline casts.
Feb. 18	600	Alkaline	1013	Faint trace	+	Hyaline casts.
Feb. 19	900	Neutral	1013	Faint trace	+	Leukocytes.
Feb. 20	900	Neutral	1016	Faint trace	0	Leukocytes.
Feb. 21	950	Alkaline	1017	Faint trace	0	Leukocytes.
Feb. 22	1800	Acid	1011	Faint trace	0	Leukocytes.
Feb. 23	1500	Acid	1012	Faint trace	0	Pus cloud.
Feb. 24	2400	Acid	1014	Faint trace	0	Pus cloud.
Feb. 25	800	Alkaline	1015	Faint trace	0	Pus cloud.
Feb. 26	400	Acid	1012	Faint trace	0	Leukocytes.
Feb. 27	550	Acid	1015	Faint trace	0	Leukocytes.
Feb. 28	425	Alkaline	1016	Faint trace	0	Leukocytes.

Phenolsulphonephthalein excretion on February 12, 51 per cent.
Phenolsulphonephthalein excretion on February 28, 55 per cent.

Case IV.—Admitted November 11. On the night of admission the patient took two 7.5-grain bichloride tablets; she arrived in the hospital in less than an hour, when the stomach was washed out. The past history was negative, except that one year before she was treated for two months for "kidney trouble."

Physical Examination. The right kidney is distinctly palpable, otherwise negative.

November 11. Mercury present in both vomitus and urine.

November 12. Treatment was started on continuous rectal irrigation by the drop method, containing potassium acetate, one-half ounce to quart of water.

November 18. Left the hospital cured, although no examination for mercury was noted at time of discharge.

Extract from urine chart:

Date.	Amount. c.c.	Reaction.	Specific gravity.	Albumin.	Sugar.	Microscopic.
Nov. 11	...	Acid	1015	Trace	0	Many hyaline casts.
Nov. 12	1770	...	...	...	..	No blood, no casts.
Nov. 13	2440	Acid	1005	0	0	Few leukocytes.
Nov. 14	4070	Acid	1005	0	0	Few leukocytes.
Nov. 15	4320	Acid	1010	0	0	Few leukocytes.
Nov. 16	3630	Alkaline	1010	Trace	0	Few leukocytes.
Nov. 17	1340	Alkaline	1010	0	0	Few leukocytes.
Nov. 18	...	Acid	1005	0	0	Few leukocytes.

CASE V.—Admitted January 23. About one hour before admission the patient took two tablets which he thought were headache medicine. Ten minutes later he had burning pain in stomach and took a glass of milk which gave slight relief. The pain continued, he came to hospital. He vomited in examining room and was given a gastric lavage (both of which proved to contain mercury). The patient brought a tablet of the medicine with him which proved to be the ordinary 7.5-grain tablet of mercuric bichloride. On being sent to the ward, he was given another gastric lavage lasting fifteen minutes, then drank one pint of milk, one-half hour later the stomach was again washed clean (this is the lavage reported January 24 as containing mercury). He was put on milk diet, continuous proctoclysis (drop method) with potassium acetate one dram to pint of water. Potassium bitartrate solution, 8 ounces, was ordered every hour. The patient was discharged January 31.

Extract from urine chart:

Date.	Amount. c.c.	Reaction.	Specific gravity.	Albumin.	Sugar.	Microscopic.
Jan. 23	2550	...	1008	Very faint trace	0	Few leukocytes and epithelial cells.
Jan. 25	2200	Neutral	1010	Faint trace	0	Few leukocytes and epithelial cells.
Jan. 26	3100	Neutral	1008	Faint trace	0	Many leukocytes and triple phosphate crystals.
Jan. 27	3900	Alkaline	1010	Faint trace	0	Few leukocytes and epithelial cells.
Jan. 28	1025	Neutral	1010	Very faint trace	0	Few leukocytes and epithelial cells.
Jan. 29	1950	Alkaline	1010	Faint trace	0	Few leukocytes and epithelial cells.
Jan. 30	2350	Neutral	1010	Faint trace	0	Few leukocytes and epithelial cells.
Jan. 31	600	Acid	1020	Very faint trace	0	Few leukocytes and epithelial cells.

January 29, phenolsulphonephthalein test, first hour, 50 per cent.; second hour, 26.5 per cent.; total, 76.5 per cent.

Tests for mercury:

	Jan. 23.	Jan. 24.	Jan. 25.	Jan. 26.	Jan. 27.	Jan. 28.	Jan. 29.
Urine	Positive	Positive	Positive	Positive	Positive	Negative	Negative
Vomitus	Positive	—	—	—	—	—	—
Lavage	Positive	Positive	—	—	—	—	—
Stool	—	Positive	—	—	—	—	—

CASE VI.—Admitted March 26, at 5.45 P.M. *Present Illness.* At 3 P.M. the patient took four 7.5-grain bichloride tablets. Shortly after this she took some castor oil and mustard water, which made her vomit. At 4 P.M. she was seen by a physician, who gave her a thorough gastric lavage and some milk.

Past History. Patient has had an interstitial keratitis and was given two doses of salvarsan and a prolonged mercurial treatment.

Family History. One other sister had congenital syphilis. The Wassermann reaction is said to be positive in her sister and herself.

The physical examination is unimportant. The routine treatment as outlined was carried out for more than five weeks. On March 26 the vomitus and lavage water were both positive for mercury. The stools, the urine, and the gastric lavage were positive to the mercurial tests for a period of several weeks. On March 28 the first negative test occurred in the gastric lavage. On May 2 the first negative test was found in the urine. On May 16 the stool was negative for the first time. The mercury was not completely eliminated by July 3, and occasional positive results were found up to that date, when the examinations were stopped.

Extract from urine chart:

Date.	Amount. c.c.	Reaction.	Specific gravity.	Albumin.	Sugar.	Microscopic.
Mar. 27	396	Acid	1010	Faint trace	0	Hyaline and granular casts.
Mar. 28	137	—	—	—	—	—
Mar. 29	45	—	—	—	—	—
Mar. 30	45	—	—	—	—	—
Mar. 31	2	—	—	—	—	—
April 1	55	—	—	—	—	—
April 2	396	—	—	—	—	—
April 3	853	—	—	—	—	—
April 6	1462	Neutral	1010	Faint trace	0	Few leukocytes; hyaline casts.
April 11	660	Alkaline	1015	Marked trace	0	Few leukocytes.
April 13	1310	Neutral	1010	Trace	0	Pus cells.
April 30	3991	Alkaline	1002	Very faint trace	0	Few leukocytes.
May 10	4640	Neutral	1005	Very faint trace.	—	Few leukocytes.

The phenolsulphonephthalein excretion in two hours was as follows: April 7, 3.3 per cent.; April 9, 4 per cent.; April 17, 41 per cent.; April 23, 47.5 per cent.; May 10, 71.4 per cent.

The striking feature in this case is that on March 31 there was an almost complete suppression, when the twenty-four-hour secretion was only 32 minims. On March 26 the Wassermann reaction was double plus and on April 24 it was four plus.

Case VII.—Admitted April 9. *Present Illness.* Four days ago the patient took one 7.5-grain bichloride tablet; the only symptom complained of is that she vomited a little later. Twenty-four hours ago she took two more 7.5-grain tablets, and about an hour later had pain in the abdomen for which she took some "soda." After this she vomited several times. About three o'clock this afternoon, she swallowed another 7.5-grain bichloride tablet, and vomited about half an hour later. The bowels have moved several times a day for the last few days, but she has felt fairly well since taking the first tablet except for a burning sensation in abdomen, and headache and has had no appetite. She has noticed no decrease in amount, or change in character of urine.

Physical examination is unimportant. The routine treatment was given and continued for two months, although the symptoms of poisoning were practically absent after the first days of gastric irritation. The tests for mercury were positive for many days both in the urine and the stools and the gastric lavage. The first negative examination in the urine was on April 27, and in the feces on June 8. But the mercury was not completely eliminated by July 3. Occasional positive results were obtained up to that date, whdn the examinations were stopped.

Extract from urine chart:

Date.	Amount. c.c.	Reaction.	Specific gravity.	Albumin.	Sugar.	Microscopic.
April 10	1175	Acid	1010	Faint trace	0	Many leukocytes.
April 12	600	Alkaline	1010	Very faint trace	0	Many leukocytes.
April 13	1600	Neutral	1015	Faint trace	0	Many leukocytes.
April 17	3500	Alkaline	1005	Trace	0	Many leukocytes; mucus.
April 30	—	Alkaline	1010	Very faint trace	0	Few leukocytes.
May 10	—	Neutral	1015	Very faint trace	0	Many leukocytes.
May 20	1500	Neutral	1010	Faint trace	0	Many leukocytes.
May 22	—	Neutral	1010	Trace	0	Many leukocytes.
June 7	—	Acid	1005	Very faint trace	0	Many leukocytes.
June 22	—	Neutral	1005	Faint trace	0	Many leukocytes.
June 23	1800	Neutral	1015	Trace	0	Few leukocytes.
June 28	—	Alkaline	1005	Trace	0	Few leukocytes.
July 1	—	Acid	1015	Trace	0	Few leukocytes.

The phenolsulphonephthalein excreted in two hours was as follows: April 9, 66.5 per cent.; April 21, 62.5 per cent.; June 22, 65 per cent.

Case VIII.—Admitted June 14. *Present Illness.* About an hour and a half before admission to the hospital the patient took by mistake six 7.5-grain bichloride tablets dissolved in water in mistake for a sleeping mixture. She drank a glass and a half of water after this. In a few minutes she felt great discomfort in her throat and vomited a large amount. She was given three raw eggs; a doctor was called, and she was sent to the hospital. Her physical examination was negative. The routine treatment was instituted. On June 14 the urine was positive to the mercury test, but the gastric lavage on admission was twice negative. It became positive on June 15 and remained so until June 17, after which it was negative. On June 23 the urine was negative for the first time, and on July 20 the first negative stool was examined. The elimination of mercury was not complete at time of discharge on July 28.

Extract from urine chart:

Date.	Amount. c.c.	Reaction.	Specific gravity.	Albumin.	Sugar.	Microscopic.
June 14	1098	Alkaline	1025	Very faint trace	0	Mucus.
June 16	2650	Alkaline	1005	Very faint trace	..	Many leukocytes.
June 22	5667	Neutral	1005	Faint trace	..	Few leukocytes.
June 24	4692	Alkaline	1005	Very faint trace	..	Few leukocytes.
June 28	8196	Alkaline	1010	0	..	Few leukocytes.
July 1	—	Alkaline	1016	Trace	..	Few leukocytes, hyaline and granular casts.
July 4	5911	Alkaline	1005	0	..	Few leukocytes.
July 6	6764	Alkaline	1005	Faint trace	..	Few leukocytes.
July 9	—	Alkaline	1020	Very faint trace	..	Few leukocytes.
July 11	5484	Alkaline	1005	0	..	Few leukocytes.
July 14	—	Alkaline	1005	0	..	Few leukocytes.
July 17	4916	Alkaline	1010	0	..	Few leukocytes.
July 19	4052	Alkaline	1005	0	..	Few leukocytes.
July 23	—	Alkaline	1005	Faint trace	..	Few leukocytes.

On June 14 the phenolsulphonephthalein excretion in two hours was 55.5 per cent., and on July 14 it was 45.7 per cent. On July 14 the Wassermann reaction was 2+ in spite of the excessive dose of the mercury.

Case IX.—Admitted July 11. *Present Illness.* About three hours before admission the patient took one 7.5-grain tablet of bichloride of mercury by mistake for aspirin. He went to the doctor's office immediately and in about fifteen minutes was given mustard and vomited several times. The stomach was then washed out throughly and patient drank milk. After that he was

sent to hospital. Distress in abdomen followed the lavage, but there was no actual pain. The bowels are regular, the urination is normal, the appetite good.

Physical examination was negative and the routine treatment was begun. On July 11 the urine, stool, vomitus, and lavage were all positive to mercury. On July 24 the first negative urine was found, but there were no negative stools before leaving the hospital.

Extract from urine chart:

Date.	Amount. c.c.	Reaction.	Specific gravity.	Albumin.	Sugar.	Microscopic.
July 11	1950	Acid	1010	Very faint trace	0	Few epithelial cells, hyaline casts, and granular casts.
July 12	3930	Neutral	1005	Faint trace	0	Few epithelial cells, hyaline casts, and granular casts.
July 13	3656	Neutral	1005	0	0	Epithelium.
July 14	4204	Acid	1010	Very faint trace	0	Epithelium.
July 15	2833	Acid	1015	Very faint trace	0	Epithelium.
July 16	3900	Acid	1010	Very faint trace	0	Epithelium.
July 17	3929	Acid	1013	Faint trace	0	Epithelium.
July 18	4288	Acid	1010	Faint trace	0	Epithelium; occasional granular cast and mucus.
July 19	2986	Neutral	1005	Very faint trace	0	Epithelium; occasional granular cast and mucus.
July 20	4022	Neutral	1005	Very faint trace	0	Epithelium; occasional granular cast and mucus.
July 21	2376	Neutral	1005	Very faint trace	0	Epithelium; occasional granular cast and mucus, and leukocytes.
July 23	3686	Neutral	1005	Very faint trace	..	Epithelium; occasional granular cast and mucus, and leukocytes.
July 24	...	Alkaline	1020	Faint trace	..	Epithelium; occasional granular cast and mucus, and leukocytes.

On July 24, phenolsulphonephthalein test showed 55.8 per cent. excretion in two hours.

CASE X.—Admitted March 21. The patient took by mistake three tablets of bichloride of mercury dissloved in six ounces of water, as a gargle, and swallowed practically all of it. She vomited fifteen minutes later a greenish fluid. Pain in the epigastrium followed immediately and patient came at once to the hospital where she vomited again, a thick, foamy, colorless mucus. The patient came under treatment within an hour after poisoning. There were no symptoms after the first two days and the treatment was routine. She was discharged on March 31. All the excreta and stomach washings were positive to mercury for three days. The stomach washing was first negative on March 24 to be again positive on March 27. The urine was first negative on March 24 and positive at intervals until treatment ceased on March 31. The colon irrigations were positive until March 30.

Extract from urine chart:

Date.	Amount. c.c.	Reaction.	Specific gravity.	Albumin.	Sugar.	Microscopic.
March 22	2737	Acid	1025	Faint trace	0	Pus cloud.
March 24	3107	Alkaline	1010	Faint trace	0	Many leukocytes.
March 26	3107	Alkaline	1010	Very faint trace	0	Occasional granular cast.
March 30	3778	Acid	1010	Very faint trace	0	No casts.

DISCUSSION

DR. THOMAS MCCRAE: My experience has been in entire agreement with that of Dr. Lambert in the treatment of bichloride poisoning, and the management we have devised is much the same as his. I should like to ask if he thinks there may be any danger in giving so much fluid in the anuric stages? In cases observed by me, there did not seem to be any harm done by this. An interesting question is, How often permanent injury to the kidneys remains in these cases? I also have found great variability in the duration of the excretion of mercury. Patients who come under this treatment soon after taking the poison have a very good outlook for recovery.

Dr. M. Howard Fussell: Dr. Lambert spoke of the erroneous impression in the minds of the public that death from bichloride of mercury poisoning is painless. A woman came under my care who had taken seven bichloride tablets; she was in such agonizing pain that morphine did not relieve her, and it was necessary to give ether; this, however, could be given only intermittently, as it induced respiratory failure. She died in twelve hours.

Dr. Samuel W. Lambert: In reply to the question of Doctor McCrae, I would say that I have never observed any injury resulting from the exhibition of large quantities of fluid in bichloride cases; that none of the patients gave evidence of permanent injury to the kidneys, although one patient had almost total anuria, and in several the output fell to four or five ounces; and that all recovered.

RESULTS OF OVERACTIVITY OF THE CERVICAL SYMPATHETIC[1]

By W. B. CANNON, M.D., and R. FITZ, M.D.
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Interest in the bodily changes during or following emotional excitement led us to inquire concerning the nature of certain diseases often reported as having emotional origin. We proceeded on the theory that repeated emotional experiences might lower a naturally high neurone threshold and thus result in frequent stimulation of parts which normally are only occasionally roused to special activity. To test the effect of overstimulation Mr. C. A. L. Binger and one of us (W. B. C.) fused in the cat the anterior root of the right phrenic nerve with the right cervical sympathetic cord. Thus after regeneration had occurred, there was delivered to neurones in the superior cervical ganglion a volley of impulses every time the animal breathed. The operations were performed early in May, 1914. In October four of six animals were still alive. All had peculiar symptoms. There was marked tachycardia—the average heart-rate in 36 observations on normal cats was 165, in 30 observations on these animals it was 222. Though fed like normal animals they had loose movements of the bowels. They suffered from falling of the hair from the neck and back, and they acted as if afflicted with pruritus of the head and toes. They were unusually excitable, as indicated by rushing away when taken in hand or petted. One of us (R. F.) has studied the basal metabolism, and found that the average heat loss per square meter of body surface per hour in normal adult cats is 31 calories; in two

[1] Aided in part by a grant from the Proctor Fund.

of the experimental animals it rose as high as 56 calories, and in one (in all ways the most profoundly altered animal) it rose to 72 calories—an increase over the normal of more than 130 per cent. This animal died after very rapid loss of weight. At autopsy the adrenal glands were found nearly three times the average size. In dim light the pupil in these animals was larger on the operated side, and in one of them exophthalmos and respiratory hippus had developed on that side. These symptoms are, in the main, characteristic of exophthalmic goitre, as seen in man. From one animal in which the metabolism rose from 25 calories per square meter per hour to 46 after the nerve fusion, the thyroid gland was removed. In two weeks the metabolism had dropped steadily to 35 calories.

The observations on these animals are preliminary to a more extensive study of the subject. The method of using the phrenic as a source of stimuli is now being applied not only to the thyroid gland but also to other organs innervated by the autonomic system. We have planned a series of studies on overaction of the autonomic, to be carried out by use of this method.

DISCUSSION

Dr. S. Solis Cohen: I see some pictures of adrenal cross sections. Were they from Dr. Cannon's cats? I should like to hear something about the kidney changes; Dr. Cannon did not mention this. I should like to inquire also, what was the condition of the thyroids of the experimental cats? As a clinician, I have held, in opposition to contemporary doctrine, the older view that the thyroid is not the primary factor in Graves' disorder and certain other conditions with which enlargement of the gland may be associated, but that the thyroid changes, functional and structural, are themselves the result of autonomic disturbance. The nature and causation of this last, which includes both nervous and secretory factors, I do not now intend to discuss. But if this view be correct, hyperthyroidism is not the main disorder, but merely one element in a complexus of considerable obscurity. The experiments reported should help to throw light on the question, and do, I presume, support the position outlined.

Dr. Walter B. Cannon: We removed part of the thyroid from some of our animals. One with considerable increase of metabolism had the right lobe of the thyroid removed, with subsequent progressive decrease of metabolism. But the thyroid is not alone involved in these animals: the adrenals are also much enlarged, even to three times the normal gland weight. As to the histological appearance of the thyroid, there are distinctive changes, but indicative of overactivity or of atrophy secondary to overactivity. The characteristic changes described in human cases have not been seen, possibly because of the high connection of the phrenic with the cervical sympathetic which leaves out the influence of the inferior cervical ganglion, this influence being the production of vasodilatation. There will be further experiments with the anastomosis made below the inferior cervical ganglion; new observations under these conditions should be more nearly like human cases.

If the theory of a low threshold for nervous impulses holds, then we can conceive of a vicious circle by which overstimulation of the thyroid causes still more overstimulation. We could then conceive of numerous ways to cut off the overstimulation: By extirpation of part of the gland; by excising nerves, etc. We need to consider also, however, the effect of the enlarged adrenals in these cases, for thus another vicious circle by way of the blood stream might be established.

THE ISOLATION OF A TOXIC SUBSTANCE FROM THE BLOOD OF UREMIC PATIENTS

By NELLIS B. FOSTER, M.D.
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(By Invitation)

The evidence which has been cited to substantiate the current conception of uremia as a toxic state is insufficient. Other than analogy with some toxic psychoses the thesis rests on the experiments of Herter, showing that the blood of patients with uremia appears more poisonous to dogs than the blood of normal persons. If there be a noxious substance in the blood of uremic patients, justifying the term "toxemia," it should be possible by appropriate chemical procedures to isolate the substance and demonstrate its action on animals. Accepting this hypothesis then, its demonstration rests on the finding of a suitable chemical method which must be not only delicate but must also exclude the use of energetic reagents capable of disintegrating the protein molecules in blood. After considerable experimentation it is believed that a technic has been found which avoids these dangers and facilitates the isolation of a substance from uremic bloods which is toxic and which is not present in other bloods examined.

It is hardly conceivable that an actively poisonous substance circulating in the blood during life would be found in other than low degrees of concentration; but there should be sufficient material in 200 c.c. of blood to kill a guinea-pig, considering the relative weight of man to a pig as 300 to 1. This criterion obtained throughout this investigation.

Uremia is somewhat diverse in its manifestations and there is a growing tendency to subdivide the clinical complex into several

types, the causation of which may be, and possibly is, different. The one distinctive feature that demarks these types is the presence or absence of convulsive attacks. Thus far study has been confined to eclamptic or epileptiform uremia.

The method of isolation of the specific substance is based on procedures commonly used for the separation of toxic bases. The blood is drawn into citrate solution to prevent clotting and is then diluted with water and the proteins precipitated with either tannic acid or, better, meta-phosphoric acid. There results a water-clear filtrate which gives no biuret reaction. Phosphoric acid is removed with barium hydrate and the latter by a stream of CO_2. The final filtrate is treated with equal parts of hot saturated solutions of sodium acetate and mercuric chloride. The resultant precipitate is filtered off and digested in 1 per cent. hydrochloric acid and again filtered. From the filtrate the mercury is removed with hydrogen sulphide. The mercury-free filtrate is condensed to a small volume at a temperature not exceeding 50° C. and then extracted repeatedly with absolute methyl alcohol. From the methyl alcohol solution the alcohol is removed by evaporation at low temperature and the residue digested with absolute ethyl alcohol; this process is repeated until all of the residue dissolves readily in alcohol. The final alcohol solution is treated with alcoholic solution of auric chloride. After standing some time there is a sparse crystalline deposit which is separated from the mother liquor and freed of gold with hydrogen sulphide. The material after drying in a dessicator is dissolved in salt solution and is ready for the animal test by injecting into the peritoneal cavity of a guinea-pig.

This procedure has been conducted with samples of blood from seven uremic patients and twelve controls; the latter comprising various diseased conditions to be mentioned later.

First with regard to the symptoms of poisoning observable in in the animals receiving the product from uremic bloods. All of these animals died within a short period after the dose was administered; whereas none of the controls was apparently made sick. The symptoms noted in the pigs receiving the toxic base were dyspnea, which gradually became more marked; violent muscular twitchings or generalized convulsive seizures, coma, and

death. The temperature was always subnormal. In two of the animals convulsions occurred within ten minutes and death within fifteen minutes. In some of the others the effect was less stormy and there was gradual lapse into a stuporous state with death in about four hours. With these animals where the symptoms developed slowly there was a paresis or paralysis of the hind legs to be noted if the animals were urged to move across a table. With all there was frequent defecation, with some diarrhea. Autopsy on these animals disclosed some hyperemia of the kidneys and brain, but nothing else of significance.

It is evident that especial care must be exercised in controlling studies of this sort by comparison with bloods from patients free of uremic symptoms. Twelve samples of blood have been examined. These have included besides normal blood, specimens from cases of severe nephritis without evidences of uremia, pneumonia, cases of coma due to cerebral hemorrhage, gas poisoning, cerebral embolism, and a case with convulsions of epileptic origin; and finally, since it seemed possible that a specific toxin might bear some relation to the obscure phenomena preceding death, a specimen of blood from a patient *in extremis* incident to valvular disease was tested. With none of these bloods was crystalline material secured, and accordingly the total final extract was administered to the test animals. In no case were there evidences of severe intoxication; no animal died.

In conclusion, then, it appears from evidence based on the study of seven cases of convulsive uremia and twelve cases used as controls, that the blood in this type of uremia contains a toxic substance peculiar to this morbid state.

The amount of this material recovered has been insufficient for analytical study and concerning the nature of the body it is possible to make no satisfactory statement at present. That the toxin is a base is evidenced by its reaction with such reagents as phosphomolybdic acid and some of the alkaloidal reagents.

DISCUSSION

Dr. L. G. Rowntree: I should like to ask Dr. Conner what the figures were for non-protein nitrogen and rest nitrogen in the uremic cases from which Dr. Foster isolated the crystalline compound.

Dr. Theodore C. Janeway: Dr. Foster's work in isolating a distinct poison from the blood of uremic patients of the eclamptic type is most important, particularly so because of the two types of uremia recognized by clinicians, one, the eclamptic, is characterized by symptoms suggestive of poisoning by an alkaloid, which class of drugs the substance isolated by Dr. Foster resembles. The other, the chronic type, is usually associated with nitrogen retention and seems to depend on poisons of another type. I hope Dr. Conner will tell us whether the cases from which this poison was obtained were hypertensive, since high blood-pressure regularly accompanies acute eclamptic uremia.

Dr. Lewis A. Conner: I cannot answer Dr. Rowntree's inquiry accurately as I have not the figures at hand, but I can say that the non-protein nitrogen and rest nitrogen were estimated in these uremic cases and in all it was increased. All of the cases were hypertensive and nearly all died in six months from the time of the examination. Several had albuminuric retinitis. Several came to autopsy.

PRESENT-DAY TREATMENT AND PROGNOSIS IN DIABETES

By ELLIOTT P. JOSLIN, M.D.
BOSTON

It is no exaggeration to say that the advance in the actual treatment of diabetes mellitus during the twelve months just passed has been greater than in any year since Rollo's time, and it should be emphasized that this improvement in treatment comes not by chance, but as a result of patient scientific experimentation, which has been based upon the work of the foremost investigators in both laboratory and clinic. It follows experiments upon animals, and is an answer to those critics who have claimed that animal experimentation in diabetes had failed to justify itself. At the same time better and simpler technical methods for the study of the blood, urine, and respiratory exchange, as well as new knowledge of the metabolism of diabetes, have contributed a share to this improvement. The truthfulness of the foregoing is easily shown. One year ago physicians were generally afraid to teach their patients to test their urines for sugar; today the physician feels himself to so much greater an extent master of the disease that this is one of the first steps to be taken.

The advantage of maintaining the urine sugar-free has been universally recognized, but all have conceded that this was impossible without danger from acidosis and inanition. Fasting and a low diet have been known, but it is only fair to give Allen the credit of first to see the therapeutic significance of inanition upon a severe case of diabetes, second to prove upon diabetic dogs that prolonged fasting would render them sugar-free, and third to have the courage of his convictions and apply this principle to human diabetes. Thanks to Dr. Frederick M. Allen, we no longer nurse diabetics—we treat them!

A review of all my private cases of diabetes, undertaken for this special purpose, has convinced me that prolonged fasting has produced results far and away ahead of any methods which I have hitherto employed. For myself, I consider the impression which I have thus obtained of far more value than any statistics which my records afford, but it is almost my duty to present these as well.

TABLE I.—CASES UNDER OBSERVATION MAY 1, 1914, TO MAY 1, 1915

Cases.	Total.	Traced.	Dead.		Alive.	
			No.	Per cent.	No.	Per cent.
Total	211	211	31	14.7	180	85.3
Old	75	75	11	14.7	64	85.3
New	136	136	20	14.7	116	85.3
Fasted	55	55	6	10.9	49	89.1
Not fasted	156	156	25	16.0	131	84.0

Old cases are those first seen prior to May 1, 1914; new cases are those first seen after May 1, 1914.

TABLE II.—AGE AT DEATH OF FATAL CASES

Cases.	Total.	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80
Old	11	0	1	0	1	2	2	1	4
New	20	3	2	3	0	3	6	1	2

As a matter of fact, I have seen 211 cases (75 old and 136 new) of diabetes in the twelve months from May, 1914, to May, 1915. All of these have been traced and are available for statistics. (See Tables I and II.) Of these 31 are dead, a mortality of 15 per cent. Fifty-five of the 211 cases were fasted and of these 6 died—a mortality of 11 per cent. In this paper I will discuss the causes of death of fatal cases among the number fasted. Case No. 648 was the first case I fasted, and I simply kept her sugar-free a part of one day in May and then allowed her gradually to return to her former diet. She died in coma June 16, 1914. Case No. 707 was my second case to undergo fasting, and he never actually became sugar-free. He at once returned home, broke all dietetic restrictions, and died in forty-six days of coma. I had not then gained sufficient confidence in the treatment to impart it to the patients and to prevail upon them to carry it through to the end. Today there is no need of that, for one patient laughs the other

half through the fasting days. Another death was Case No. 855, aged seventy years, onset at fifty-eight years, weight 220, who was first seen by me four days after an operation for appendicitis, during which, unfortunately, a large quantity of ether was employed. Despite fasting, which for the most of the time had been nearly absolute, he never became sugar-free. He died of heart failure, without coma, but probably associated with a necrosis of the cells of the liver and pancreas. Case No. 764 was fasted after leaving my supervision by another physician. The patient broke treatment, exercised unusually, and died promptly in coma. He lived some four hundred miles from Boston, and seven miles from the physician in attendance, and was that physician's first case. Case No. 576 was fasted. He died of recurrence of cancer in the scar of the abdominal incision forty-seven days after the growth had been removed from the bladder by Dr. Chute. Case No. 430, who developed diabetes in June of 1908, at the age of fifty-two years, came under my observation in July, 1911, and was fasted for a day in September, 1914. He returned to Canada and died on March 12, 1915, of diabetic coma. The other 49 cases which have been fasted are alive.

Corroborative evidence of the value of Dr. Allen's ideas is the gratifying fact to me that the last death to occur while the patient was under my personal supervision in a hospital was on August 29, 1914. That patient, Case No. 758, had a blood-pressure of 215, and died of coma. Since that date 48 cases have been treated by me in hospitals without a death.

The study of the respiratory quotient of two groups of fatal cases of diabetes and another group of living cases furnishes evidence which is worthy of mention. These investigations were made at the Nutrition Laboratory of the Carnegie Institution in conjunction with Professor Francis G. Benedict, and are illustrated in Tables III and IV. In the first group of fatal cases with a respiratory quotient of 0.71, the duration of life following the period of observation varied between forty-four and fourteen days. In another group of eight fatal cases with the somewhat higher respiratory quotient of 0.74, the duration of life under similar conditions varied from four hundred and forty-two to seventy days.

In comparison with these groups of fatal cases, there is a group of four cases still living. The average respiratory quotient of these four cases was 0.715, but the duration of life had already reached, up to May 1, 1915, from eight hundred and sixty-two to one hundred and thirty-four days. These patients are now (June 1, 1915) all alive and are in good condition. Furthermore, they have been treated along lines employed by Dr. Allen.

TABLE III.—RESPIRATORY QUOTIENT IN SEVERE DIABETES

Year.	Cases.	Observers.	R. Q.
1894	1	Weintraud and Laves	0.70
1897	2	Nehring-Schmoll	0.72
1905	2	Magnus-Levy	0.71
1907	1	Mohr	0.72
1908–1911	19	Benedict and Joslin	0.73
1912	8	Rolly	0.74
1912	3	Grafe and Wolf	0.74
1912–1914	7	Benedict and Joslin	0.73

TABLE IV.—RESPIRATORY QUOTIENT IN FATAL AND LIVING CASES OF SEVERE DIABETES COMPARED

Fatal cases.			Four living cases.		
No. of cases.	Days before coma.	R. Q.	Case number.	Days before May 1, 1915	R. Q.
6	44–14	0.71	552	862	0.72
			765	187	0.73
			786	173	0.71
8	442–70	0.74	806	134	0.70
				862–134	0.715

The behavior of the various types of diabetes under fasting and a low diet is not quite uniform. The mild and moderately severe cases have done well and time has been saved in the initial treatment. A good many of the moderately severe cases who frequently showed sugar now keep sugar-free easily, and this has contributed much to their peace of mind. Both conditions may be attributed to the patients having learned to test their own urines. Children have been particularly favorable subjects, although I cannot say that I have a case under treatment which has exceeded that of Case No. 74, a duration of three years and eleven months, which is my record fatal case, or five years and two months, which is my record case still alive for a child with an onset under fifteen years.

Complications of pruritus, carbuncles, and abscesses have cleared up better than formerly, and so did one case with neuritis.

A woman, Case No. 812, six months pregnant and with 6.4 per cent. of sugar, under a low diet—not fasting—became sugar-free, was delivered by Cesarean section by Dr. J. C. Hubbard, and both baby and patient are now,[1] eight weeks later, in good condition. Other patients have been operated upon successfully for cancer of the uterus, cancer of the bladder, removal of prostate, amputation for gangrene and for extensive carbuncles.

The results are divergent with long-standing cases. In one notable case, Case No. 801, of ten years' duration, there is no question but that the improvement has been marked, and now he lives comfortably on a diet of 45 grams carbohydrate or less and attends to his customary occupation. Incidentally, the recovery from a carbuncle which led to his first coming to me for treatment was unusually prompt. But another case, Case No. 352, of twenty-one years' duration, who was not doing well, although he has become sugar-free, has a tolerance of only 10 to 15 grams carbohydrate. His weight is maintained after an initial loss of four and one-half pounds, but he is weak. I think that his strength will return, but the blood sugar varies between 0.14 per cent., 0.19 per cent., and 0.27 per cent., although no complicating nephritis is present.[2] Another patient, Case No. 664, has steadily lost weight, and although she feels fairly comfortable, is weak. Perhaps I should treat this last patient more rigorously—perhaps the diseased pancreatic function is really becoming exhausted. Sometimes it almost seems as if a patient with diabetes, as well as his friends, felt injured if his span of life was not prolonged further than that of a healthy individual. There is no question but that many of the patients of a severe type are less vigorous for some weeks after the fasting period is over than before it began, when they were excreting sugar. In a number of cases time enough has elapsed to show that strength is regained, but this is not universal Perhaps I look for too quick results. However, it would not be fair to say to an active diabetic doctor, with a rather severe type of diabetes, that if he followed this plan of treatment he could return to a strenuous practice in three or four weeks. Of course he ought not to have a

[1] October, 1915, in good condition and sugar free.

[2] This patient has continued to improve, looks well and rides horseback. July, 1915.

strenuous practice, but all of us know that many such physicians do. On the other hand, it would be perfectly correct to say, if you follow this plan of treatment there is little doubt but that you will live longer, only you must live at a reduced rate.

There remains the type of disease with severe acidosis, and for these patients this form of treatment is almost universally successful. Table V on page 159 illustrates this point.

Unfortunately, in none of the severe cases has there been any decided gain in tolerance, although there have been deceptive apparent gains.

The advantages of the new treatment are many. It has made attainable the ideals of treatment—namely, a sugar-free and acid-free urine. The standards of the success of treatment are so simple that they are within reach of the patient. At one stroke the patient is delivered from medicines, patent and otherwise, sham kinds of treatment, gluten breads, and in 99 cases out of 100 of alkalies. He can now test all measures for himself. Consider the amount of time and money saved both doctor and patient in urinary tests.

The hospital stay is not particularly shortened, except indirectly by the avoidance of complications, because the patient requires a more thorough education in the diet. It does simplify general hospital treatment, because so soon as a diabetic patient in an open ward shows sugar, it will generally mean that he has broken his diet, for which the automatic penalty is a fast until sugar-free. Unquestionably complications will become less frequent, and it is possible that arteriosclerosis will less commonly occur in the long-standing cases as a result of the restricted diet.

One of the greatest benefits which will be derived from the new method of treatment is the basis which it will give for new lines of experimental work. The question of the D : N ratio should be soon settled. Already new facts have appeared as a result of the study of the metabolism of these patients, and to some of these attention is now directed.

The investigation of the metabolism of severe cases of diabetes has been continued by Professor Benedict and myself at the Carnegie Laboratory, and 19 more patients have been studied since September 1, 1914. The first notable change which we observed

TABLE V.—CASE NO. 740. MALE. ONSET IN MAY, 1914, AT TWENTY YEARS AND TEN MONTHS

Date 1915	Body weight.	Volume of urine.	Reaction.	Total nitrogen.	NH_3-N	Acetone and diacetic acid.	Diacetic acid. (Qual.)	Beta-oxybutyric acid.	Dextrose (Grav.)	Diet.					Blood sugar.	Alveolar air CO_2 tension.	CO_2 per kilo per min.	O per kilo per min.	R. Q.	Calories per kilo per 24 hours from O_2.
										Carbohydrate.	Protein.	Fat.	Alcohol.	Calories.						
	Kilos.	c.c.		gms.	gms.	gms.		gms.	gms.	gms.	gms.	gms.	gms.	gms.	%	m.m.	c.c.	c.c.		
March 27	54.0	3000	Acid	32.70	5.60	..	++++	..	74											
April 14–15 ($14\frac{1}{4}$ hrs.)	52.9	1430	Acid	12.44	2.64	3.11	+	19.99	40	..	..	..	0							
April 15–16	52.2	1540	Acid	16.48	3.16	3.69	+	18.33	39	15	50	70	0	890	0.26	24.1	2.91	4.05	0.72	27.5
" 16–17	51.7	1420	Slightly acid	16.20	3.28	3.09	++	13.41	45	17	55	75	0	963	0.43	29.5	3.02	4.16	0.73	28.2
" 17–18	52.1	900	Acid	9.63	2.44	2.00	+	8.23	16	0	7	0	24	196	0.26	31.4	2.94	4.08	0.72	27.6
" 18–19	51.7	680	Acid	8.10	2.15	1.79	++++	7.85	8	0	6	0	0	24	0.33	31.0	2.84	3.88	0.73	26.3
" 19–20	50.6	580	Slightly acid	6.72	1.73	1.29	+++	5.59	3	0	0	0	24	168	0.29	31.6	2.88	3.77	0.76	25.7
" 21–22	51.5	540	Slightly acid	7.94	1.57	1.18	++	4.40	0	0	5	0	24	188	0.24	32.1	2.71	3.62	0.75	24.6
" 24–25	51.6	570	Acid	9.06	1.57	1.09	+++	3.65	Trace	5	20	25	18	451	0.31	30.8	2.61	3.54	0.74	24.1
" 27–28	50.9	640	Slightly acid	7.36	1.02	0.91	+	3.10	Trace	0	2	0	15	113	0.31	30.6	2.74	3.67	0.75	25.0
May 1.	50.4	945	Slightly acid	7.56	0.74	0.83	0	2.64	Trace	0	2	0	15	113	0.28	32.9	2.61	3.44	0.76	23.5

was an upward tendency of the respiratory quotient in these cases following the institution of a fast. This became so marked that we had doubts about the accuracy of the respiration apparatus which we employed. A new apparatus, devised by Dr. Benedict, but not yet described, was also employed, and with this the results were essentially the same. Still more recently we have confirmed our data with the Tissot apparatus and the bed calorimeter.

In January we compared the results which Dr. Du Bois obtained with two of Dr. Allen's patients, and noted that in his laboratory a similar tendency had been recorded. Table V illustrates this increasing respiratory quotient and other changes in the metabolism. The patient was Case No. 740, a young man in whom the onset of the disease occurred at the age of twenty years and ten months in 1914. He showed, nineteen days before the first test, 5.6 grams of ammonia nitrogen in twenty-four hours, and 74 grams sugar in the urine upon a diet supposedly containing but a few grams of carbohydrate. In June he was sugar-free and at work.

It will be noted that the respiratory quotient was 0.72 upon the first day of observation, but gradually rose to 0.76 upon the last day. If one calculates the non-protein respiratory quotient, it will be seen that this also rose, and it is obvious that notable quantities of carbohydrate, or some material with a high respiratory quotient, must have been burned following the starvation treatment. This remarkable phenomenon is hard to explain. Has the diabetic patient actually more carbohydrate in the body than is commonly supposed? Could the rising quotient be due to combustion of acid products, of which the respiratory quotients for acetone, diacetic acid, and beta-oxybutyric acid are 0.75, 1, and 0.89 respectively? The chart shows that if a diabetic is fasted acidosis disappears, and this is in marked contrast to the behavior of normal men, for they present acidosis upon fasting with no increase in the respiratory quotient as the fasting proceeds.

The metabolism at the beginning of the experiment was 18 per cent. higher than at the end. Coincident with this decrease in the metabolism was the fall in acidosis. It appears, furthermore, logical to conclude that if the metabolism had been estimated a few days prior to the first experiment when the acidosis was greatest

of all, amounting to 5.6 grams ammonia-nitrogen, the metabolism would have been still greater. The normal metabolism for this patient lay probably somewhere between the metabolism first and last recorded, and one would not be far wrong to estimate it at the beginning of the test at 10 per cent. above normal and at the end at 10 per cent. below normal. The significance of the fall in metabolism with the decrease in acidosis is striking.

The chart is also instructive in that the falling metabolism bears no relation whatsoever to the blood sugar, for this was essentially the same throughout. It is interesting that the calories per kilo per twenty-four hours, as calculated from the oxygen inhaled, amounted to approximately 28 to 24 per day, and that the calories given the patient during the latter part of the period were approximately this same figure. Subsequent days have confirmed the observation that this patient when sugar- and acid-free can hold his weight at a little less than 30 calories per kilogram body weight.

The method which has been employed in the treatment of these cases has been similar to that recommended and described by Dr. Allen. The more closely his directions have been followed the better the patients have done. No patient has required more than five days to become sugar-free. Many patients became sugar-free after the omission of three or four meals. Patients are put to bed and the plan of treatment is carefully explained to them. They are furnished with note-books in which answers to their questions are recorded, taught the use of a diet card and how to examine the urine for sugar with Stanley R. Benedict's solution. As a working basis the general plan of treatment is summarized below, and for convenience the following diet chart, printed on a card five by three inches, has been used.

Fasting. Fast until sugar-free. Drink water freely and one cup tea and one cup coffee if desired. If sugar persists after two days of fasting, add in divided portions 300 c.c. clear meat broth.

Alcohol. If acidosis (diacetic acid) is present, take 0.5 c.c. alcohol per kilogram body weight daily until acidosis disappears. Alcohol is best given in small doses every three hours.

Carbohydrate Tolerance. When the twenty-four-hour urine is sugar-free, add 150 grams of 5 per cent. vegetables and continue to add 5 grams carbohydrate daily up to 20 grams, and then 5 grams every other day, passing successively upward through the 5, 10, and 15 per cent. vegetables, 5 and 10 per cent. fruits, potato, and oatmeal to bread, unless sugar appears or the tolerance reaches 3 grams carbohydrate per kilogram body weight.

Protein Tolerance. When the urine has been sugar-free for two days, add 20 grams protein (three eggs) and thereafter 15 grams protein daily in the form of meat until the patient is receiving 1 gram protein per kilogram body weight; or if the carbohydrate tolerance is zero, only $\frac{3}{4}$ gram per kilogram body weight. Later, if desired, the protein may be raised to 1.5 gram per kilogram body weight.

Fat Tolerance. While testing the protein tolerance a small quantity of fat is included in the eggs and meat given. Add no more fat until the protein reaches 1 gram per kilogram (unless the protein tolerance is below this figure), but then add 25 grams fat daily until the patient ceases to lose weight or receives not over 40 calories per kilogram body weight.

Reappearance of Sugar. The return of sugar demands fasting for twenty-four hours or until sugar-free. The diet preceding the reappearance of sugar is then resumed except that the carbohydrate should not exceed half the former tolerance until the urine has been sugar-free for two weeks, and it should not then be increased more than 5 grams per week.

Weekly Fast Days. Whenever the tolerance is less than 20 grams carbohydrate, fasting should be practised one day in seven; when the tolerance is between 20 and 50 grams carbohydrate, 5 per cent. vegetables and one-half the usual quantity of protein and fat are allowed upon the fast day; when the tolerance is between 50 and 100 grams carbohydrate the 10 per cent. and 15 per cent. vegetables are added as well. If the tolerance is more than 100 grams carbohydrate, upon the weekly fast day the carbohydrate should be halved.

Strict Diet. Meats, Fish, Broths, Gelatin, Eggs, Butter, Olive Oil, Coffee, Tea and Cracked Cocoa

Foods Arranged Approximately According to Per Cent. of Carbohydrates.

VEGETABLES

5 per cent.		10 per cent.	15 per cent.	20 per cent.
Lettuce	Cauliflower	Onions	Green peas	Potatoes
Spinach	Tomatoes	Squash	Artichokes	Shell beans
Sauerkraut	Rhubarb	Turnip	Parsnips	Baked beans
String beans	Egg plant	Carrots	Canned lima beans	Green corn
Celery	Leeks	Okra		Boiled rice
Asparagus	Beet greens	Mushrooms		Boiled macaroni
Cucumbers	Water cress	Beets		
Brussels sprouts	Cabbage			
	Radishes			
Sorrel	Pumpkin			
Endive	Kohl-rabi			
Dandelions	Broccoli			
Swiss chard	Vegetable marrow			
Sea kale				

FRUITS

Ripe olives (20 per cent. fat)	Lemons	Apples	Plums
Grape fruit	Oranges	Pears	Bananas
	Cranberries	Apricots	
	Strawberries	Blueberries	
	Blackberries	Cherries	
	Gooseberries	Currants	
	Peaches	Raspberries	
	Pineapple	Huckleberries	
	Watermelon		

NUTS

Butternuts	Brazil nuts	Almonds	Peanuts
Pignolias	Black walnuts	Walnuts (English)	
	Hickory	Beechnuts	40 per cent.
	Pecans	Pistachios	Chestnuts
	Filberts	Pinenuts	

MISCELLANEOUS

Unsweetened and unspiced pickles, clams, oysters, scallops, liver, fish roe

Reckon *actually available* carbohydrates in vegetables of 5 per cent. group as 3 per cent., of 10 per cent. group as 6 per cent.

30 grams, or 1 ounce, of each of the following contain approximately:	Protein, grams.	Fat, grams.	Carbohydrates, grams.	Calories.
Oatmeal, dry weight	5	2	20	110
Meat (uncooked)	6	2	0	40
Meat (cooked)	8	3	0	60
Broth	0.7	0	0	3
Potato	1	0	6	30
Bacon (cooked)	5	15	0	155
Cream, 40 per cent.	1	12	1	120
Cream, 20 per cent.	1	6	1	60
Milk	1	1	2	20
Bread	3	0	18	90
Butter	0	25	0	240
Egg (one)	6	5	0	75
Brazil nuts	5	20	2	210
Orange (one)	0	0	10	40
Grape fruit (one)	0	0	10	40
Vegetables, 5–10 per cent. groups	0.5	0	1	6

1 gram protein, 4 calories.
1 gram fat, 9 calories.
6.25 grams protein contain 1 gram nitrogen.
30 grams (g) or cubic centimeters (c.c.) = 1 ounce.
A patient "at rest" requires 25 to 30 calories per kilogram body weight.

1 gram carbohydrate, 4 calories.
1 gram alcohol, 7 calories.
1 kilogram = 2.2 pounds.

Bread is seldom prescribed, because it is so easy for a patient to overstep the limits. Many patients use bread substitutes, such as Huntley & Palmer's Akoll Biscuits, Barker's Gluten Flour[1] (Brand A), Hepco Flour,[2] Lyster Bros'. Diabetic Flour.[3] The quantity of fat which it is necessary to give a severe case is considerable. A diabetic weighing 60 kilograms requires at least about 30 calories per kilogram body weight to be up and about the hospital, with an occasional walk. Since in the severe cases not more than 10 grams carbohydrate, representing 40 calories, can be given in this form, and seldom more than 75 grams protein (1.25 grams per kilogram body weight), which would amount to 300 calories more, the balance of the diet must be made up of 150 grams fat, amounting to 1350 calories, and even more unless 15 grams alcohol are given, which would amount to 105 calories.[4]

TABLE VII.—QUANTITY OF FOOD REQUIRED BY A SEVERE DIABETIC PATIENT WEIGHING 60 KILOGRAMS

Food.	Quantity grams.	Calories per gram.		Total calories.
Carbohydrate	10	4	=	40
Protein	75	4	=	300
Fat	150	9	=	1350
Alcohol	15	7	=	105
		Total	=	1795

The quantity of fat (150 grams to 160 grams) is easily given in the form of 120 c.c. of 40 per cent. cream (48 grams), 15 grams of oil (15 grams); and 3 eggs (15 grams), bacon (cooked) 30 grams (15 grams), meat (cooked), 100 grams (5 grams), and butter 60 grams (50 grams). These figures are only approximately correct.

Should the patient remain sugar-free and the weight be maintained upon this diet, gradually the quantity of fat could be lowered and the carbohydrate increased. A very few of my patients have a tolerance for between 200 and 300 grams of carbohydrate. With most the tolerance is below 100 grams, and with the majority it is under 50 grams.

[1] Herman Barker, 433 Broadway, Somerville, Mass.
[2] Waukesha Health Products Co., Waukesha, Wisconsin.
[3] Lyster Bros', Whitefield, New Hampshire.
[4] It is quite possible that considerably less food is required. October, 1915

The patient should have one day of restricted diet each week no matter how mild the case. This is done partly to spare the function which controls the carbohydrate metabolism, but also to remind the patient of what a strict diet really is. The patient is told to gain little or no weight, and as Dr. Allen advises, not to come up to his former weight. The severer cases examine the urine daily, and the milder ones once a week. The patients are instructed to lead less strenuous lives. Unfortunately, they feel so well that often this advice is disregarded, and I believe that all of us err in allowing our patients to do too much. They should have nine hours in bed at night, and should have a quiet hour of rest each day, no matter how well they feel.

Patients must be followed up. The secret by which this is brought about lies in instructing the patient how to live in the first few days of treatment, and making him understand that he must always be under supervision. This is sometimes difficult, for a doctor does not like to force a patient to come to him. Fortunately, improvement in the treatment of diabetes is rapid enough to enable a physician to repay his patient for a visit with new ideas at comparatively short intervals.

The after treatment of diabetic patients is quite as important as the initial treatment. Patients must learn to keep sugar-free and maintain weight, and when difficulties occur report for advice. There is not the slightest doubt, in my opinion, that even under the old regime the patients who were kept under judicious supervision did better than those who neglected treatment.

Many dangers suggested themselves when I commenced to use the fasting treatment, but most of these have gradually faded away. It is still true that a patient who undertakes the treatment and then relapses to former slack methods is worse off than his untreated brother. Liability to infection is not common. A child, Case No. 813, of eight years, acquired tonsillitis and developed an otitis media, but this was a circumstance not unusual for any hospital patient. In another direction an unlooked-for danger has appeared. Owing to the apparently easy control of diabetes, several diabetic married women have seen no reason why they should not become pregnant. So far I have treated but one case under the new regime.

and that patient did well. How other patients will do I cannot predict.

More difficulties will arise in the introduction of the newer methods of treatment from the physician than from the patient. Physicians who have only an occasional case of diabetes under their care, and in general mild ones, will not take the time or see the necessity of keeping their patients sugar-free. It is the same experience with which we all are familiar in pulmonary tuberculosis. A number of physicians who have had serious cases have become interested and investigated the treatment, and these report excellent results. In several instances fasting has been carried out most successfully by the family physician at home. The difficulty will arise in prevailing upon the physician to carry out protracted fast in the severer types of the disease. This takes real courage, and it is desirable that all who have had good results with severe cases should publish their reports. The doctor in the hospital clinic can easily handle the patient, but it takes time to educate the family and all the friends.

No one can tell how well diabetic patients will do in the future. It is surprising to me to note how much better my patients have done during the last six months, and to note that those cases which have followed most carefully the restricted diet and fasting have done the best. So far no patient whom I have taught to examine his own urine during the last year has died. I am coming to feel that coma no longer represents the culmination of the disease, but that it is an avoidable accident.

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PROLONGED FASTING IN DIABETES

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(By Invitation)

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Partial pancreatectomy, with preservation of the pancreatic duct so as to avoid atrophy of the remnant, gives a more satisfactory reproduction of clinical diabetes than is afforded by von Mering and Minkowski's total pancreatectomy or Sandmeyer's method of slow pancreatic atrophy. Simple lowering of the sugar tolerance without diabetes, or diabetes varying in intensity from the mildest to the very severe, can thus be produced at will. As previously pointed out,[1] animals thus prepared constitute valuable test-objects and afford favorable opportunities for research concerning diabetic therapy. In the milder types the measures ordinarily used in human diabetes, namely, restriction of carbohydrate or protein, and brief fasting if necessary, suffice to keep the animals sugar-free and in good condition indefinitely. But in a more severe type these measures do not suffice and the animal quickly passes into a hopeless condition if more radical treatment is delayed. In this type the initial fast must sometimes be measured in weeks rather than in days. The subsequent diet must be such as to keep the animal at a low level of weight and metabolism. Certain influences which increase either weight or metabolism tend to bring back glycosuria in these animals as in human patients. If glycosuria persists in any animal the result is a downward sequence of lowered tolerance, emaciation, weakness, cachexia, and death, with parallel degenerative changes in the islands of Langerhans. If glycosuria is prevented, the animals may remain lively and strong though thin;

[1] Allen, F. M., Studies Concerning Glycosuria and Diabetes, Harvard University Press, Cambridge, Massachusetts.

they may improve somewhat with time, and the islands seem to be spared. This evidence supports the hypothesis that one set of influences overtax and injure the internal function of the pancreas, and the opposite set of influences protect and rest the internal function of the pancreas.

The treatment of diabetes at the Rockefeller Hospital has been based upon these animal experiments. The patients admitted have been forty-four, chosen as the most severe out of a considerable number of applicants, and representing a sufficient variety as respects age, social condition, and other factors. Certain points may here be mentioned concerning (1) the initial fast and (2) the subsequent diet.

Fasting has been employed by writers from Naunyn to Guelpa. The same writers describe a numerous class of diabetics who are not made sugar-free, but go on with glycosuria and acidosis and die in coma. Other patients are made sugar-free only after months of strict dietary treatment, including occasional single or repeated fast-days. Present experience indicates that the glycosuria in cases of even the severest type of diabetes may with advantage be cleared up by one initial fast. The necessary duration may sometimes be as long as eight or ten days. In one case of maximum severity in a youth, aged seventeen years, the changes accompanying fasting were studied by Dr. Eugene Du Bois in the respiration calorimeter. He found that at the outset the total metabolism was about 8 per cent. above normal and the patient was excreting all or nearly all of the sugar formed from protein and burning practically no sugar at all. In a nine days fast the glycosuria ceased, the total metabolism fell to about 20 per cent. below normal, and the respiratory quotient showed that the sugar formed from protein was being burned. It will be remembered that respiratory quotients in the most severe cases during the "oat cure" do not show increased combustion of carbohydrate. The above metabolic observations are new and constitute important evidence for the functional element in the etiology of human diabetes, since they show to what extent recovery can take place within a few days when the most complete possible rest is given the weakened metabolic function.

Severe acidosis, which is known to be diminished by the shorter fasts previously employed, is still more reduced by the more prolonged fasting. Dangerously weak and emaciated patients have borne the fasting with apparent benefit, giving the impression that they had been suffering more from intoxication than from lack of nutrition. Alcohol is valuable during fasting as a food which does not produce glycosuria, though its use is not essential. Broadly speaking, freedom from glycosuria seems attainable in all cases of uncomplicated human diabetes before there is danger of death from starvation. In a few cases seen personally or described by others, death from some severe complication has occurred before the urine became sugar-free. In such cases to date the complication has been a severe infection, or some condition strongly tending to increase metabolism or produce nervous or circulatory disturbance. The fasting has not appeared harmful even in these few cases where it has not been successful. One case of incipient gangrene and one dangerous carbuncle cleared up rapidly under fasting, and threatening complications of infectious or any other character are considered an indication for the radical treatment as described. No contraindication has been met, unless it be the appearance of nausea, vomiting, and prostration while fasting. One woman died in such an attack; but there were attacks of this character in her previous history, and it is not positive that either the attack or the death was due to the fasting. One man began to vomit and feel unwell on the seventh day of fasting. He was fed and the symptoms immediately passed off. After two weeks of restricted diet a second fast easily cleared up the glycosuria. This simple precaution apparently prevents danger even in this rare type of cases, and in other cases there has never been any sign of danger or harm.

Though the initial fast, to clear up glycosuria and other symptoms, is generally a very simple matter, the subsequent diet, to maintain this condition, is sometimes difficult. It is unquestionably true, in accord with Joslin's[1] warning, that when glycosuria is abolished and strength diminished by long fasting, and then glycosuria and acidosis allowed to return through improper diet, the last state

[1] Discussion of paper at meeting of Suffolk County Medical Society in connection with Boston Medical Library, December 2, 1914.

of that man may be worse than the first. Herein may be found the causes of failure in past attempts of this sort. After the fasting patient has been completely sugar-free for one or two days, feeding is begun as outlined in former papers,[1] and the tolerance of the patient for carbohydrate, protein, and fat is determined. Just as fasting is continued not for any limited number of days, but as long as necessary for sugar-freedom, so also the diet is governed not by any theoretical standard of protein or calories, but by the amount of each food that can be given in each individual case while keeping the urine clear. Under this program even weak and emaciated patients have been subjected to under-nutrition in both protein and calories for weeks or months continuously, with ultimate benefit. Any trace of glycosuria is the signal for a fast-day with subsequent modification of diet, and routine fast-days are often used as frequently as once a week even in absence of glycosuria. While individual details must be reserved to a later publication, two principles in the management of severe cases may be mentioned, namely, the benefit of keeping the patient permanently below weight, and the advisability of restricting the quantity of fat in the diet.

A slight temporary reduction of weight was practiced in some cases by Naunyn, whose example has been widely followed. This was not carried to the point of abolishing glycosuria and acidosis in the severest cases; and generally the attempt has been to maintain these patients at the highest possible level of weight and nutrition, with the idea of helping them to withstand a wasting disease. The present idea is the opposite to this, namely, that the reduction of weight is in itself beneficial to the diabetic condition and serves to spare the weakened function and increase tolerance. This measure, like the others, is carried to any point that may be necessary in any particular instance. Sometimes a slight reduction of weight suffices even for a severe case. Again, a well-nourished patient, easily kept free from glycosuria, was reduced by twenty kilograms merely because of a slight stubborn ketonuria and a

[1] Allen, F. M., Jour. Amer. Med. Assoc., September 12, 1914; Boston Med. and Surg. Jour., February 18, 1915; New York State Journal of Medicine, 1915, xv, 330 to 333.

persistently high blood-sugar. Most patients are able to regain weight to a greater or less extent, but few severe ones are able to return fully to normal weight. Any increase that is possible without return of symptoms is permitted. Any gain that brings back glycosuria or ketonuria is checked. The experience in human patients thus far runs parallel to that in the animal experiments upon which this suggestion was founded.

In the treatment of diabetes heretofore, fat has been freely given and even forced upon the patient. It has been restricted only in certain cases with high acidosis and danger of coma. The doctrine has been that fat does not affect diabetic glycosuria except in very rare "fat-sensitive" patients; also, that the diabetic must receive the number of calories required by his metabolism, plus the number of calories lost as sugar and acetone bodies in the urine, and fat has been considered the best food for crowding in these calories. Anyone can readily convince himself that, in a suitably severe diabetic who is symptom-free for days or weeks on a fixed diet, the addition of some quantitiy of butter or olive oil to the diet will bring back the glycosuria, ketonuria, and other symptoms immediately or within a short time. The feeding of fat alone does not cause glycosuria, and there is no proof that the sugar is formed from the fat; more probably the sugar excretion results from the stimulating effect of fat upon metabolism. The overtaxing of the patient's metabolism by giving fat beyond the limit of tolerance may be an additional explanation of the failure to keep certain patients free from glycosuria and ketonuria under former methods of treatment.

Concerning any proposed treatment, inquiry is proper whether it is new and whether its results are superior to those of the old methods. The following statements can be made regarding these points.

The principle tentatively suggested that increase of weight or metabolism increases strain upon the internal pancreatic function and reduction of weight or metabolism reduces strain upon the internal pancreatic function, is new, and if it proves valid will be a useful general guide in treatment. The animal experiments likewise are entirely new. The general policy of insisting upon prompt

and lasting freedom from glycosuria and acidosis in all cases of diabetes, even the severest, is a new one. In addition, the main features wherein the proposed treatment differs from the previously established methods may be summarized under the following five headings. The first two represent differences merely of degree, in that the proposed treatment is more radical than the old; namely, first, an initial fast sufficient to clear up glycosuria in any case and then one or two days longer; second, a subsequent diet such as to keep glycosuria and acidosis permanently absent, with as many interspersed fast-days as necessary for this purpose. The third and fourth features represent differences not in degree but in kind, and are diametrically opposed to the prevalent teachings; that is, the third opposes the idea that the diabetic should be kept at the highest possible level of weight and strength, and that gain in weight is synonymous with improvement; and it substitutes for this the plan of keeping most severe diabetics intentionally and permanently at a sufficiently low level of weight and metabolism, in the belief that return of symptoms and downward progress is thus prevented. The fourth feature stands opposed to the doctrines that fat feeding does not appreciably influence diabetic glycosuria, and that calories lost in the urine should be replaced by additional calories in the diet, preferably in the form of fat. It opposes to these the observation that addition of fat to a fixed diet suffices to bring back both glycosuria and ketonuria in most severe diabetics, and the principle that the patient's tolerance for fat and calories should be followed in the same way as the tolerance for carbohydrate and protein. The fifth feature consists merely of routine or incidental matters, which are not without practical importance. Among these may be mentioned (1) the diet such as not to overtax tolerance and yet satisfy the patient sufficiently that he will follow it continuously at home; (2) the absence of any specific craving for carbohydrate such as diabetics are supposed to manifest, and the contradiction of the prevalent idea that most severe diabetics cannot be trusted; (3) the avoidance of the need of alkali for more than a few days, and therewith relief from disturbances due either to acidosis on the one hand or to prolonged large doses of soda on the other; (4) the principle of clearing up the urine quickly and devot-

ing the greater part of the stay in hospital to educating the patient, rather than devoting the greater part of the stay in hospital to clearing up the urine and dismissing the patient shortly thereafter; (5) instruction of the patient in the simple means of controlling his own condition, through his diet, his body weight, and the daily testing of his own urine with Benedict's solution.

The immediate results as observed up to the present have appeared uniformly beneficial. Reports from a number of clinicians experienced in the older methods of treating diabetes agree that these results under the new method are more favorable. Also the relative simplicity of the proposed method, and the fact that it stops glycosuria without running any risk of acidosis, makes it available for a large body of general practitioners who have heretofore not felt safe in withdrawing carbohydrate or attempting to stop glycosuria in cases with any marked ketonuria. Patients also generally accept radical treatment with quick decisive results more readily than the weeks or months of privation heretofore used in stopping glycosuria, and the quick relief from polyphagia, polydipsia, and other symptoms aids further in securing their coöperation. For these reasons it is believed that the innovations described are of some real value. As respects the remote results and the influence on the ultimate prognosis of severe diabetes, longer experience must decide. A question is here involved whether diabetes is an inherently progressive disease or whether it is the simple weakness of a metabolic function. If it is the former, patients must ultimately go down hill and die, though not in diabetic coma, and the benefit will consist only in lengthening their lives and keeping them more comfortable. If it is the latter, downward progress may be indefinitely prevented by avoiding overstrain of the weak function, just as in animals. Among the patients treated thus far, during a variable number of months in the hospital and at home, spontaneous downward progress has not yet been observed. Whatever the ultimate outcome, two conclusions seem justified by present knowledge: (1) that this treatment removes glycosuria and acidosis more quickly and surely than has been the practice heretofore, and (2) that patients do better when glycosuria and acidosis are removed than when they are allowed to continue.

A STUDY OF THE ACIDOSIS OCCURRING IN THE NUTRITIONAL DISEASES OF INFANCY

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In the course of severe diarrhea in infancy, especially in fatal cases, there frequently are seen stupor merging into coma and disturbances of respiration which may amount to severe dyspnea. The dyspnea is not dependent upon cardiac or renal disease and is unaccompanied by cyanosis. We have made observations upon many cases with severe or prolonged diarrhea and have to record the following findings:

1. Many infants with a severe watery diarrhea show a marked reduction in the CO_2 percentage of the alveolar air. So far as can be made out clinically the more severe the symptoms, especially if associated with dyspnea, the lower the CO_2 percentage. We have used a modification of the Plesch method:

No.	Date.	CO_2 Mm.	Dyspnea.	Alkali.
I	Sept. 22	20.6	+++	Given.
I	Sept. 23	41.2	0	Given.
I	Sept. 24	53.1	0	Stopped.
I	Sept. 25	40.2	0	
II	Sept. 28	17.9	+++	Given.
II	Sept. 28	17.5	+++	Given.
II	Sept. 29	20.8	++	Given.
II	Sept. 30	33.6	+	Given.
III	Sept. 27	27.1	++	Given.
III	Sept. 28	30.0	+	Given.
III	Sept. 29	35.2	0	Given.
IV	Nov. 16	32.6	+	Given.
IV	Nov. 17	36.8	+	Given.
IV	Nov. 20	57.8	0	Stopped.
IV	Nov. 24	46.9	0	
IV	Dec. 2	44.2	0	
V		27.4	++	
VI		29.6	++	
VII		23.7	+++	
VIII		26.1	++	

2. A diminution of the alkalinity of the serum as shown by Sellards' test. In this test the protein-free alcoholic filtrate is evaporated to dryness with phenolphthalein. Sellards found that with the acidosis of diabetes and uremia a colorless residue is obtained which is in marked contrast to the deep purple color normally obtained. We have found in severe cases an absolutely colorless residue.

3. We have determined in a few cases the hydrogen ion concentration of the blood serum, using the dialysis indicator method devised by Marriott and Rowntree. We have found this at times increased so that, for example, in two cases it was 10 to 7.2 and and 10 to 7.4, whereas in the normal it varies from 10 to 7.6 to 10 to 7.8. This indicates a marked and dangerous reduction of the alkalinity of the serum.

4. The scanty urine passed by these infants in very acid, and remains so in spite of massive doses of soda given by mouth, subcutaneously or intravenously. This is in accord with the observations of Sellards and of Henderson and Palmer who found a very great tolerance in acidosis for soda.

5. By giving alkalies we have been able to cause, in several instances, a cessation of the dyspnea, a return of the CO_2 tension to normal or even abnormally high limits, and return of the hydrogen ion concentration of the blood to normal. (See Table.)

6. We have observed recovery in several instances after energetic treatment by alkalies, only, however, when the condition was recognized early. The recognition can be made most sharply and readily by the determination of the CO_2 tension of the alveolar air. If treatment is postponed until the development of increased pulmonary ventilation, sufficiently marked to be recognized as dyspnea, the possibility of recovery is greatly reduced even though by treatment with alkalies the normal alkalinity of the blood and the normal CO_2 tension of the alveolar air may be brought about.

The diminution of the CO_2 tension of the alveolar air is the first indication of the abnormal, the positive Sellards' test and the increase of the hydrogen ion concentration of the blood are later indications of a very severe acidosis.

7. No acetone bodies have been found in the urine.

The cases that we have studied have been clinically those called "Toxicose" by Czerny or "Alimentäre-Intoxikation" by Finklestein. Czerny, in 1898, called attention to the similarity between the dyspnea in such cases and that produced in rabbits by mineral acids. Finklestein has categorically stated that the symptoms are due to the products of intermediary metabolism imperfectly catabolized. No definite proof of their claims has been advanced.

In the light of our observations upon the CO_2 tension of the alveolar air, upon the hydrogen ion concentration of the blood, upon the test of Sellards, upon the increased alkali tolerance and upon the effect of alkali therapy, it seems quite clear that a very important—if not the most important—element in producing the condition is an acidosis. It is very likely that this is the result of the loss of alkali by the bowel which has been shown by Steinitz to be responsible for the high ammonia content of the urine in severe diarrhea.

MILD DIABETES IN CHILDREN

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The fatality of diabetes in early life is an axiom that has come down to us through generations of text-books as a hoary tradition.[1] However, an increasing number of observations seems to show that juvenile diabetes need by no means be a mortal disease—that in childhood and youth, as in adult life, diabetes may run a favorable course.

Case I.—For several years I have had under observation a boy and a girl—brother and sister—who when they first came to me gave me great concern. The boy, aged nineteen years, had been urged by his father to take out life insurance in order to learn lessons in economy. Though he believed himself perfectly well, he was rejected, naturally to his great consternation, because sugar was found in the urine. Before he came to me another physician had confirmed this fact and had given a gloomy prognosis. The boy had had no sickness of moment, except a mild attack of jaundice four years previously. I placed him on a carbohydrate-free diet, but the sugar persisted for a long time. There was usually a trace present at some time during the day, frequently in the morning specimen. The quantity of urine was not increased and there was no thirst. Indeed, aside from loss of weight, probably due to restriction in the food intake, the boy presented nothing abnormal, except a profound mental depression, for which a chance question gave me an explanation. I learned that a medical student had told him that diabetes in the young was absolutely hopeless. The sugar, tested by the reduction and the fermentation method, varied,

[1] Since reading this paper, the statistics of De Lange and Schippers (Nederlandsch Tijdschrift voor Geneeskunde, 1915, July 24, ii, No. 4, p. 637) have appeared. They found between 500 and 600 cases of diabetes in children recorded; recovery was mentioned in only 30 of the 500 cases, and these were not traced long. They themselves report 8 cases in detail. All terminated fatally, the duration varying from 8 or 9 months to 2 years and 5 months.

as is shown in the chart, from traces to 0.6 per cent. Diacetic acid was never present. Without any other than dietetic treatment the boy finally lost his glycosuria, and no longer excretes sugar, though on a normal diet.

Case II.—Shortly after the first case came under my observation, the boy's sister, seventeen years old, presented herself on account of loss of flesh—in a few months her weight had dropped from 133 to 122½ pounds. She had thirst at times and a poor appetite. Menstruation was painful, but regular. Her color was pale—hemoglobin 70 per cent. The urine contained glucose from a trace to 0.7 per cent. The quantity varied from

URINE CHART.—CASE I

Date.	Quantity.	Reaction.	Specific gravity.	Albumin.	Sugar per cent.	Remarks.
Dec. 24, 1910	....	Alkaline	1040	—	Considerable	Diacetic acid. 0.
Dec. 29, 1910	....	Acid	1027	—	Distinct	
Jan. 5, 1911	1500	Acid	1030	—	Distinct	
Jan. 12, 1911	2500	Acid	1025	—	—	
Jan. 14, 1911	2000	....	....	...	Trace	
Jan. 19, 1911	1750	Acid	1018	—	Trace	
Feb. 16, 1911	2375	....	1030	—	Trace	
June 10, 1911	....	Acid	1030	—	Trace	
July 13, 1911	....	Acid	1029	—	—	Oxalates.
Aug. 8, 1911	....	Acid	1019	Faint trace	Trace	
Dec. 11, 1911	2000	Acid +	1028	Trace	0.6	Urates; oxalates.
Dec. 27, 1911	....	Acid	1026	—	0.6	Oxalates.
Jan. 11, 1912	1650	Acid	1030	—	0.55	Oxalates.
May 18, 1912	....	Acid	1020	—	Trace	Diacetic acid, 0.
May 21, 1912	....	Acid	1034	—	Trace by fermentation	Diacetic acid, 0.
Nov. 8, 1913	....	Acid	1010	—	0.5	

URINE CHART.—CASE II

Date.	Quantity.	Reaction.	Specific gravity.	Albumin.	Sugar per cent.	Remarks.
Jan. 2, 1911	....	Acid +	1033	—	Trace?	
Jan. 19, 1911	....	Acid	1040	—	Trace	
Jan. 23, 1911	1500	Acid	1030	—	Trace	
Jan. 30, 1911	1000	....	....	—	Distinct	
Mar. 7, 1911	....	Acid	1025	—	Trace	
Mar. 25, 1911	1250	Acid	1030	—	Trace	
May 27, 1911	1000	Acid +	1032	—	Trace	Diacetic acid, 0.
Oct. 22, 1911	....	Acid	1030	—	0.6	Diacetic acid, 0.
Oct. 29, 1911	....	Acid	1021	—	0.4	Diacetic acid, 0. Acetone, 0.
Feb. 3, 1912	....	Acid	1019	—	0.7	
April 3, 1912	....	Acid	1030	—	0.55	
May 26, 1912	....	Acid	1023	—	0.3	

1000 to 1500 c.c. in the twenty-four hours. (See Chart.) On a strict diet her weight fell to 110½ pounds, a reduction of 22½ pounds from her maximum weight. After ten months the weight began to increase, having reached when the patient was last seen 128¾ pounds. Coincident with this increase there was an improvement in her general condition, the hemoglobin rising to 84 per cent. The sugar has disappeared from the urine.

A few months ago she was married and is living in the middle west enjoying the best of health.

Case III.—The third patient is E. W., aged twenty-two years, the eldest brother of the two preceding. Aside from an attack of jaundice at thirteen, he had always been well. At any rate, though attending his family for many years, I scarcely knew him professionally until August, 1911, when he came because he was losing weight. Examination of the urine showed a trace of sugar. He apparently recovered, for I did not see him again until November 6, 1913, when shortly after returning from his wedding trip he began to suffer from attacks of indigestion. His appetite was good, but he refrained from eating on account of the distress that followed. He had noticed that at the height of an attack he would pass a colorless urine. I again found a trace of sugar, although there was no polyuria, no thirst, no real diabetic symptoms. The digestive disturbances yielded promptly to treatment. I have not seen him for eighteen months, but know from his family that he is to all appearances perfectly well.

There is no diabetes in the parents of these patients, nor in collateral relatives. A maternal aunt has gall-stones. The other five children (there are eight altogether) are, as far as I know—and at some time or another I have examined every one—free from glycosuria. The parents are exceedingly nervous, and the whole family, except the first patient, are very fond of sweets—so much so that the candy box is never closed.

Case IV.—R. C., a girl of fourteen years, born in Russia, has a mother who has been diabetic for nine years. The child was well until three weeks before coming to the Polyclinic Hospital. At that time the mother noticed that she drank more water than usual, and passed urine oftener and in larger amounts, getting up from one to four times a night. She also had a little pruritus vulvæ, mostly on urination. Measles and a possible attack of whooping-cough constitute all her previous illnesses. She has been a steady candy eater. Menstruation began at thirteen and has been regular and rather profuse, lasting eight days. The father and the other children—a brother and a sister—appear to be well. Physical examination of the child shows nothing abnormal. She weighs 88 pounds, which is a loss of 7 pounds since the beginning of her illness. The blood examination gave the following results: Red blood cells, 4,850,000; hemoglobin, 88 per cent.; leukocytes, 12,600; polymorphonuclears, 61 per cent.; lymphocytes, 38 per cent.; eosinophiles, 1 per cent.; color index, 0.91.

In this patient the diabetic taint is more pronounced than in the others (see Chart, Case IV), yet under dietetic restriction she has not only become sugar-free, but has attained a tolerance of 90 grams of carbohydrate.

DIABETIC CHART.—CASE IV

Date.	Quantity urine c.c.	Total calories per diem.	Grams dextrose in urine.	Grams dextrose in diet.	Weight.	Remarks.
Feb. 7, 1915	1200	1450	12	18	84¼	
Feb. 10, 1915	969	1500	11	18	85	
Feb. 11, 1915	900	1500	0	12	85	
Feb. 21, 1915	1475	1350	6	11	86½	
Feb. 25, 1915	1500	1640	3	135	86¼	Oatmeal day.
Feb. 26, 1915	850	380	0	28	86¾	Green day.
Feb. 27, 1915	860	340	0	24	...	Green day.
Feb. 28, 1915	850	240	0	33	86	Green day.
Mar. 1, 1915	1400	340	0	29	...	Green day.
Mar. 2, 1915	900	1640	0	135	...	Oatmeal day.
Mar. 3, 1915	800	1440	0	12	84⅜	
Mar. 17, 1915	1280	1450	0	12	86¼	
Mar. 21, 1915	1500	1700	0	72	88	
Mar. 24, 1915	1250	2000	0	128	89¾	
Second admission:						
April 29, 1915	750	1450	0	8	90¼	
May 1, 1915	1050	1720	0	38		
May 3, 1915	750	2000	0	68	90½	
May 5, 1915	700	1980	Faint trace	94	91½	100 grams dextrose.
May 6, 1915	650	1550	0	12		

These four cases, particularly the first three, belong to an apparently well-defined group to which Frank[1] and Salomon[2] have called attention. Among Salomon's thirteen cases, however, only two are under the age of twenty-five. He employs the term diabetes innocens im jugendlichen Alter, although several cases over thirty-five years of age are cited in his list. The salient features of the mild forms of juvenile diabetes are:

1. The familial tendency—the existence of the disease in several members of the same generation.

2. The quantity of sugar tends to be low; in Salomon's analysis usually under 1 per cent., likewise, except in Case IV, in mine.

3. Salomon found that when one hundred grams of glucose were added to the diet, only a small amount was eliminated in the urine, showing a high carbohydrate tolerance. In my fourth case, in which this test was tried, almost no sugar was recovered from the urine.

4. In many cases the blood sugar is about normal; in other words, there is no hyperglycemia.

The fourth case, the only one in which an estimation was made,

[1] Die Therapie der Gegenwart, 1914, lv, 439.
[2] Deutsche medizinische Wochenschrift, January 29, 1914, p. 217.

showed 0.1 per cent., sugar in the blood on one occasion, and several weeks later 0.149 per cent.

Ketonuria may occur in these patients under a carbohydrate-free diet, but disappears rapidly when starches are given.

The first three of my cases fit very well into the category of so-called renal diabetes. The characteristics of this form, as established by Klemperer, Lépine, Frank, and Salomon, are as follows: The diabetes is mild; the daily output of sugar varies from a trace to 1.5 per cent., and is above this only when the amount of urine is small. The glycosuria is independent of the ordinary carbohydrate intake, and the ingestion of even large amounts of carbohydrate influences the glycosuria only to a slight degree—rarely are more than 20 grams per day excreted. Although the carbohydrate intake affects the sugar output but little within the limits given, it is possible to detect a slight increase under a rich carbohydrate diet and a decrease under a sparse or carbohydrate-free diet. Under complete carbohydrate withdrawal the urine may or may not become sugar-free. The fact that in some instances it is impossible to render the patient sugar-free by a withdrawal of carbohydrate is, as Frank points out, not a sign of gravity, but is dependent upon the renal nature of the trouble.

Conclusions. 1. There exists a mild type of diabetes in childhood and adolescence.

2. The disease is peculiar in its tendency to occur in several members of the same family.

3. The glycosuria is usually moderate, although nervous excitement and other disturbing factors may augment it.

4. Other diabetic symptoms are often slight and may be wanting.

5. The disease is not progressive and may remain stationary or end in apparent recovery.

DISCUSSION

Dr. Frank Billings: I am surprised to hear it said that the method of starvation of diabetic patients is new. We have used that method in Chicago for a number of years and patients have been fasted for as long as eight days. The adoption of the method there was due to the work of Woodyatt.

A point to be remembered is that the study of patients at rest in a hospital is only part of the problem; it is necessary to study them after exercise, after return to ordinary mode of life. For years, I have taught patients how to examine their own urine. While it may be harmful to give fats in general in diabetes, butter fat is not harmful. Diabetics may take butter fat or bacon fat and may do so for years. Whatever may be said, it is impossible ever really to control diabetic patients; they will do as they please as soon as they get beyond the observation of the doctor.

Dr. Henry Koplik: I regard diabetes in children as a very grave disease and the prognosis as always bad. This is not inconsistent with the fact that these children may go along for years without symptoms; they finally relapse and therefore the prognosis should be cautious. It is surprising how easily children bear starvation and how quickly sugar disappears under this form of treatment.

Dr. A. E. Taylor: I should like to give the details of a case which illustrates the correctness of Dr. Allen's views. A man was seized with acute pancreatitis, was operated upon and a degenerating pancreas removed, leaving only the head. This man lived for six and a half years with only a moderate glycosuria. Then he went into coma, with acidosis, and soon died, but of uremia.

Dr. Henry A. Christian: Whoever is given the credit for originating the starvation method in diabetes, certainly we have received the stimulus for applying the treatment at the Brigham Hospital from Dr. Allen's work.

We usually find one or two days of starvation sufficient to get the average diabetic patient sugar-free; before starvation two days are required to establish the standard of carbohydrate utilization with three to four days needed to standardize the patient and render him sugar-free, all the other days of hospital stay may be used for education and to increase carbohydrate tolerance in the patient. Diabetes is an ideal disease with Dr. Allen's methods for the application of the class plan of management in the out-patient department. We teach our patients to follow their carbohydrate intake and output, to cook their food, to examine their own urine,

and when sugar appears to reduce their carbohydrate diet or better to starve themselves until they become sugar-free. These patients are taught to use the Benedict method, which, by the way, is incorrectly given in many of the books; too little alkali usually is specified.

Dr. L. F. Barker: One of the good things which may come out of this meeting will be the putting into the consciousness of practitioners all over the country the advantages of immediately starving patients suffering from diabetes until they are sugar-free and the acidosis is reduced.

But "hard hitting" will be necessary to dislodge the prevalent idea that carbohydrate feeding is necessary in diabetic acidosis. Only the other day, while working with one our best clinicians in Baltimore on a case of diabetes complicated by sepsis, a note came from the laboratory worker, an excellent man who made the daily urinary analyses; he urged that we begin feeding carbohydrates at once, as he feared that our sudden restriction of the diet, as shown by the reduction of the sugar output, the low urea percentage and the acidosis, was jeopardizing the patient. My colleague and I agreed that, a year earlier, we should have shared the chemist's fears, but, emboldened by the brilliant successes of Allen, we persisted in the starvation treatment for several days, and, to our gratification, the patient quickly became sugar-free and the ketonuria diminished; gradually the sepsis was overcome, a low diet was cautiously permitted, and the patient is now in better health than for a long time previous.

As to the reduction of body weight recommended by Dr. Allen, it is certainly justifiable when necessary to make the patient aglycosuric or to reduce the ketonuria. It is also advisable in every instance when the patient is obese. But it is doubtful whether it is proper to insist on this in cases with fair carbohydrate tolerance, because of the well-known harmful effects of underweight and of undernutrition on the nervous system, and on the general bodily functions. Dr. Allen will doubtless agree with me that the nearer the weight of the patient can be maintained to his calculated ideal weight, as long as there is neither glycosuria or acidosis, the better.

Dr. R. T. Woodyatt: For eight years at the Presbyterian Hospital we have regularly used starvation in the treatment of diabetes following principles with which I became acquainted in the clinic of Müller in Munich. We have fasted patients for purposes of desugarization for periods of one, two, three, and in one case five days, and have kept patients for prolonged periods in semistarvation. There can be no doubt of its value in certain phases of treatment. As to its safety, I have seen two deaths apparently from spread of infection immediately following a period of fasting.

Concerning the progressiveness of diabetes, I would differ with Dr. Allen's generality. As Naunyn says: "Diabetes is as variable in its

course as it is possible to conceive," and in every case there are periods of progress or decline. Old cases become stationary but none are so from first to last. The stage of progression may be short and overlooked. Progress is easily recognized when diabetes appears as an accident in the course of surgical infectious diseases like cholecystitis.

Dr. Lewis A. Conner: Dr. Allen spoke of the absence of sugar from the urine as the controlling index in treatment by his method; how does the blood-sugar behave? Does he attempt to maintain the blood-sugar at an approximately normal figure or is he content with merely keeping the urine sugar-free? As to exercise: If it is necessary to keep metabolism at a low level, rest must be an important detail of the treatment. I should be glad to know what Dr. Allen's practise is with regard to rest and exercise in the subsequent management of these cases.

Dr. Frederick M. Allen: Dr. Riesman's observations are interesting. The existence of mild diabetes in children shows that not all cases in childhood are necessarily rapidly fatal. There are reports in the literature of rare cases, even of severe type, in children, which have cleared up completely and remained so permanently. It is important that cases like Dr. Riesman's should be observed for years to learn their ultimate outcome. They are a basis of hope in the treatment of diabetes in childhood.

As Dr. Barker suggests, it is attempted to increase the diet as the tolerance for various foods rises. Perhaps the ultimate regimen may be a modified Chittenden diet, that is, moderately low in protein and calories, and safely below the tolerance in carbohydrate. In severe cases, especially those of long standing, we have sometimes had to keep patients on almost starvation diet for weeks or months continuously, but in the end they have acquired power to take a living diet without glycosuria.

The ideal is that the blood-sugar should be normal. It will be necessary to determine later whether this is possible in all cases. In a number of young, severe cases it has been done. Older cases may be very stubborn, and further observations must decide whether a normal blood-sugar is necessary or feasible in such patients.

Dr. Taylor's surgical case is particularly important as the only good example of surgical diabetes in a human patient. The relatively benign course may be comparable to the very slow progress or stationary tendency of certain clinical cases. The microscopic findings in such a pancreas should be particularly interesting.

In answer to claims that this mode of treatment is now new, it can be stated that such a method has at least not been described in the literature. There are published case reports showing that it has not been the custom of authors to take the severest cases of uncomplicated diabetes and make and keep them sugar-free in this manner. On the contrary, patients are

described as going on with heavy glycosuria and acidosis, and finally dying in coma. It is essential in this treatment not merely to make a patient sugar-free by fasting, but also to keep him so thereafter by suitable diet and repetitions of fasting. If glycosuria and acidosis are partially or wholly cleared up by fasting, and then allowed to return by improper diet, harm may result. The possibility is still open that very rare patients may be impossible to clear up by fasting. I have not yet seen or heard of such a case except in the presence of serious complications such as are generally fatal in themselves. Even if a patient dies of a severe infection before glycosuria ceases, the few cases yet observed have not shown any harm from the fasting. The radical treatment is indicated in threatening surgical conditions. Dr. Joslin and others have prepared patients for operation by this method, with good results. It is probable that the specific injury to nutrition represented in active diabetes lowers resistance more than the simple withdrawal of food.

Dr. E. P. Joslin: I have records of 90 cases of diabetes in individuals under twenty years of age. About two-thirds of these patients died. No patient has lived over three years and eleven months save four, and these cases have shown familial or hereditary diabetes to a marked degree. This tendency is beautifully illustrated by Dr. Riesman's cases.

RETENTION IN THE CIRCULATION OF DEXTROSE IN NORMAL AND DEPANCREATIZED ANIMALS

AND THE EFFECT OF AN INTRAVENOUS INJECTION OF AN EMULSION OF PANCREAS UPON THIS RETENTION[1]

By I. S. KLEINER, M.D., and S. J. MELTZER, M.D.
NEW YORK

The content of dextrose in the circulating blood of normal animals is almost constant; it amounts to about 0.1 per cent. The carbohydrates of the foodstuffs form the main source of dextrose in the body. On their way from the digestive tract the carbohydrates are transformed into various forms of saccharides; but all are finally converted largely into glycogen, which is stored up mostly in the liver. The blood obtains its supply of dextrose from the glycogen of the liver, and distributes it among the tissues of the body according to their demand for it. In the normal animal none of the dextrose escapes through the kidneys. Accordingly the constancy of the amount of dextrose in the blood is regulated by a mechanism which controls either of the two factors; the *supply* of or the *demand* for it.

In diabetes the dextrose content of the blood is higher than normal, is variable in amount, and, when it is sufficiently high, dextrose escapes through the kidneys. The cause of the increase of the blood-dextrose, or hyperglycemia, may be found either in a decrease in the demand of the tissues for dextrose, that is, the tissues burn dextrose less readily than in normal conditions; or in an increase in the supply, that is, the liver supplies the blood with more dextrose than in normal conditions. Both possibilities have

[1] From the Department of Physiology and Pharmacology, Rockefeller Institute for Medical Research.

groups of followers who have brought forward numerous experiments in support of either theory.

It was experimentally established years ago that the complete removal of the pancreas brings on a severe hyperglycemia, leading to considerable glycosuria and to the death of the animal. Here we are confronted again with the question, whether the presence of the pancreas in the normal animal favors the burning of the dextrose by the tissues, or whether it restricts the supply of dextrose to the blood by the liver. But there also arose another question, namely, whether the effect of the removal of that gland was due to a removal of a controlling substance, or whether it was due, in consequence of the operation, to an interference with the nervous mechanism which controls the supply of the dextrose. In case of the first alternative, namely, that the resulting hyperglycemia is due to a removal of some substance, normally secreted by the pancreas, we have to assume that that substance belongs to that group of substances which are provided by glandular and other tissues for the proper maintenance of functions of the animal body, *i. e., internal secretions,* since a complete suppression of the external secretions of the pancreas never leads to hyperglycemia or diabetes.

We wish to report briefly results of several series of experiments which are likely to shed some light upon these questions. Most of our experimental series have one feature in common, namely, that the blood was provided with dextrose directly and not by way of the liver. In one series of experiments large quantities of dextrose (20 c.c. of a 20 per cent. solution of dextrose per kilo body weight) were injected intravenously into normal dogs. It was found by us, as it was found by some investigators before us, that the injected large surplus of dextrose disappeared quite rapidly from the circulation. *Ninety minutes after the infusion, the dextrose content of the blood reached nearly the same level which it had before the injection.* About one-half of the injected quantity of dextrose left the circulation through the kidneys; the other half went into the tissues. In nephrectomized animals also the dextrose returned to the previous level in the same length of time. *Here we have a striking example of the ability and readiness of the circulation of a normal animal to rid itself of a large surplus of dextrose.*

In another series of experiments similar injections of dextrose were made into animals, the pancreas of which was removed by an operation a day or two before the dextrose infusion. The sample of blood taken from the animal before the intravenous injection of dextrose was strongly hyperglycemic. It was then found that in these experiments *the dextrose content of the sample of blood, which was taken ninety minutes after the end of the dextrose injection, was at least twice as high as that of the sample taken before the injection.* Apparently the removal of the pancreas interfered with the power of the circulation to rid itself readily of a surplus of dextrose. The possible ability of the liver to provide the circulation with a greater supply of dextrose in the absence of the pancreas can certainly be no important factor in these results. Our experiments show then, *that in the presence of the pancreas the circulation rids itself easily of intravenously introduced dextrose; but that it is unable to do it satisfactorily in the absence of the pancreas.* On the basis of these facts is it not plausible to assume further that the pancreas exerts exactly the same influence, when the dextrose in the circulation is being supplied in some other manner than by a burette into a vein, for instance, by the liver through its connections with the circulation? Or, in other words, do not our experiments make the assumption plausible that pancreatic hyperglycemia is due to the fact that *in the absence of the pancreas the circulation is unable to dispose properly of the dextrose which it receives in normal amounts from the liver*?

In a third series, the experiments were again made by injecting dextrose intravenously in depancreatized dogs. But in these cases a strained pancreatic emulsion was added to the dextrose solution, and in some instances the infusion of the pancreatic emulsion was continued for some time after the infusion of the dextrose was finished. We present here merely a preliminary communication; we have not yet mastered all the details of this part of the investigation. But there seems to be no doubt about the nature and validity of the main result, which is this: In such experiments, *ninety minutes after the end of the dextrose infusion, the dextrose content of the blood is again at about the same level as it was before the infusion of the dextrose.* Apparently the presence of

a pancreatic emulsion within the blood helps the circulation to get rid of the surplus of dextrose injected intravenously. In these experiments it is evident that the *effect of the pancreas can be only of a chemical and not of a nervous nature*, or, in other words, it is the internal secretion of the pancreas which helps the circulation to get rid of the surplus of dextrose.

To the above results we wish now to add the following preliminary statement derived from three experiments. *In depancreatized animals, the blood of which have shown a marked hyperglycemia, an intravenous infusion of a pancreas emulsion brought the dextrose content of the blood to 0.09 per cent., and even 0.08 per cent.* The hyperglycemia returned next day and could be reduced again to the normal level by an infusion of pancreas emulsion.

Conclusions. In normal animals the circulation possesses the ability to get rid readily of a surplus of dextrose injected intravenously. In the absence of the pancreas this ability of the circulation is impaired. This ability can be temporarily restored by an intravenous injection of a pancreas emulsion.

Furthermore, an intravenous injection of a pancreas emulsion is capable of reducing the hyperglycemia due only to depancreatization to a normal level of the dextrose content of the blood.

As to the nature of the factors which may constitute the ability or inability of the circulation to get rid of a certain degree of surplus of the dextrose content of the blood, we are not willing to discuss it at this stage of our investigation. We are rather bent upon seeing how many more facts we shall be enabled to bring to light on the basis of the hypothesis which set us to work on these problems.

FOUR CASES OF HEMATOMYELIA: WITH A BRIEF DISCUSSION OF THE ETIOLOGY

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Hematomyelia, or spinal hemorrhage is a sufficiently unusual condition to justify the report of cases from a purely clinical aspect and at the same time so much variation of opinion appears to exist as to the probable causation of spinal apoplexy that additional data in regard to this aspect of the problem is definitely valuable.

It was originally designed to report the following four typical instances of hematomyelia with complete microscopic studies of the tissues, and for this purpose the spinal cords were carefully segmented and fixed. Through an unfortunate occurrence the entire collection of tissues was lost and with it the notes detailing the gross appearance of each segment. For this reason it is now only possible to discuss these cases from their clinical and etiological stand-points, but these appear to be of sufficient interest to justify the writer in presenting them.

Case I.—Pilot, aged forty-six years. Had measles when young; malaria off and on for fifteen years. Gonorrhea sixteen and syphilis twenty years ago. Spasmodic drinker of beer, whisky, or anything convenient; sometimes drunk every other day. Chews and smokes. Has been always pretty well, save for several accidents.

Present Illness. Drank heavily all day, slept very well that night. Went into the saloon the next morning for a bracer. While seated in the rear room he suddenly lost himself and did not rouse until he waked in the alcoholic wards of Bellevue Hospital. Total motor and sensory paralysis below the arms, incontinence of urine and feces. Marked and increasing priapism. Paralysis ascended quite rapidly to arms. Temperature fluctuated irregularly from 96° to 104°. Pulse rate also varied greatly, not

corresponding with temperature curve but ranging from 56 to 120. Respiration entirely diaphragmatic, from 12 to 26, without reference to temperature or pulse. Pulmonary and cardiac status practically normal.

Complete loss of sensation, of temperature, pain, and touch, with complete motor paralysis below level of third dorsal nerves. Patellar, cremasteric, abdominal, and wrist reflexes entirely lost. Incontinence of feces and retention of urine. After a few days there was some regain of sensation and power in the arms and shoulders. Mentally he became perfectly clear. Patient finally sank into a comatose condition and died twenty-three days after the hemorrhage.

An autopsy was done by permission and on the assurance that only the spinal cord would be examined. A large terminal acute and an old hemorrhage was found involving the cervical and lower dorsal segments. The hemorrhage had followed down the ventricle of the cord, infiltrating out thence into the gray matter. The columns seemed to be free from the lesion. Spinal vessels sclerosed.

Case II.—J. C., salesman, aged sixty-seven years. Had bilious and typhoid fevers in 1865. One attack of gonorrhea. Syphilis denied. Two heat prostrations. Has drunk very moderately. Good and regular habits. While driving his horse on the speedway he became suddenly dizzy, turned his cart, and collided with another vehicle. Was thrown out, landing on shoulders and head. He remained unconscious for about five minutes during which he was carried to the subway and was met by an ambulance.

Examination showed no voluntary motion below the shoulders. All reflexes below the nipple line were absent. Sensation markedly decreased above this zone. Touch sensation present but markedly dull along the ulnar distribution of both arms. Sensations of heat and cold are lost. The paralysis is perfectly symmetrical. There is a small contusion over the sacrum but none elsewhere.

Respiration is entirely diaphragmatic; thorax does not move at all. Forced respiration extends to sternocleido and scaleni muscles. Temperature, 98.4°; pulse, 80; respiration, 24. Very marked continuous priapism. On the second day the patient developed first a posterior congestion of the bases of both lungs succeeded by a true pneumonic consolidation. Urine and feces incontinent. The mentality became entirely normal; the priapism disappeared.

Seven days after onset the lung status had nearly cleared, though the slight contusions and abrasions of the skin failed to heal, and showed signs of trophic ulceration. Slight movement of the chest muscles became then apparent and the movements of the upper extremities became improved and more correlated. Slight reflex, after pricking the plantar surfaces of the feet, appeared. Bowels less incontinent. Chest clearing.

Apparent improvement continued until nine days after onset, when quite suddenly the patient became very cyanotic, then unconscious. Pulse

slow and very feeble; pupils contracted; deviation of left eye; Cheyne-Stokes respiration; complete relaxation of muscles of the extremities; early death.

The autopsy was performed by permission a few hours after death. The muscles of the paralyzed extremities showed the early evidences of atrophy. Except for the contusions mentioned, there were no evidences of traumatism, no fractures or evidences of intradural or extradural hemorrhage. The superficial arteries and veins of the spinal arachnoid showed some congestion, especially in the upper cervical regions. They were moderately sclerosed.

There was a moderate general softening and a dilated ventricle from the medulla to the sixth cervical segment. Here the gray matter was soft and hemorrhagic and the dilated ventricle was filled with a bloody, grayish, pasty material. The seventh segment showed complete blood infiltration of the gray matter. In the eighth segment the hemorrhage was most marked and had a fresh appearance, especially in the posterior horns. In the first dorsal segment the hemorrhagic softening was very marked in the horns, mostly in the posterior, but in the lower half of the segment it was chiefly confined to the left crescent of the gray matter. In the second dorsal segment the softening was entirely confined to the left crescent, more in the posterior horn, but becoming less and less in the lower levels of the segment. The third dorsal segment showed the same changes in lesser degree, but with general congestion of the bloodvessels.

From this level down to the seventh dorsal there was very little disease, but here the ventricle and its adjacent tissue showed a hemorrhagic softening. The eighth segment showed a simple dilated ventricle without hemorrhage. Blood again appeared in the ventricle at the level of the tenth dorsal segment with the usual extravasation outward. A small psammoma was found attached to the posterior root, on right side, just as it was given off from the cord.

There was a small hemorrhagic area in the left posterior horn of the second lumbar segment; another such area was found located near the ventricle. The third lumbar segment showed a very similar condition. The same was found in the fourth lumbar segment, but the sacral levels showed no changes aside from a general congestion. The cauda showed no disease.

The brain showed practically nothing except for isolated patches of slight arachnoid thickening and congested and sclerosed bloodvessels. No hemorrhagic foci were found on gross examination. The arteriosclerosis, which is evidently of long standing, showed moderate calcareous changes.

The basal ganglia showed nothing, and careful sectioning of the pons, cerebellum, and medulla failed to demonstrate any gross abnormalities.

Examination of the general viscera was limited by the terms under which the autopsy was obtained. Insofar as studied they showed no lesions of importance except a patchy, pneumonic consolidation, apparently

resolving and a chronic interstitial with an acute parenchymatous nephritis. The general bloodvessels showed extensive sclerosis.

Case III.—C. J., male, aged forty years; a marble cutter, married. Had measles when a child. Fourteen years ago had a gonorrhea. Denies lues. Five weeks ago had an attack of vertigo which lasted about one week. Nine days ago, while at South Beach, the patient went to stool; being constipated he strained very hard. When he attempted to get up he found that he has lost control of his legs. He had burning pains from the thighs down until three days ago, since which he has experienced shooting pains but twice. His bowels have not moved, and he has to be catheterized. Patient has recently been working in a damp house; to this he attributes his trouble. He has been an inveterate user of tobacco, and has been moderately alcoholic.

He is well nourished, tongue slightly coated, appetite good, bowels constipated. Physical examination of the chest is negative. There is loss of sensation and motion below both knees. Imperfect sensation (heat, touch, pain) of lower one-third of thighs, scrotum, and arms. Cremastic and patellar reflexes, also ankle clonus, absent. Muscles of calves flabby; no priapism at present. Temperature, 98°; pulse, 90; respiration, 24. Mental status entirely normal.

Patient was put to bed, and in addition to general treatment was given daily massage of the paralyzed extremities. At the end of eight days he was moving the legs slightly, but he had developed a trophic ulcer over the sacrum. Sensation was greatly disturbed, but present in some degree even in the legs; distribution did not seem to be constant. Constipation was still very marked and drastic measures were required to induce movements. Cystitis no better.

Thirty-four days after admission he had regained control of the sphincters in large part, but atrophy of the involved extremities was steadily increasing. Cystitis and the bed-sore became progressively worse. He sank into an apparently septic condition, and died forty-one days after admission, fifty days after the acute onset.

The autopsy was performed eighteen hours after death. Body extremely emaciated. Extreme atrophy of both legs, especially of the anterior tibial groups. No atrophy of the muscles of the upper extremities or of the thorax or abdomen. The heart showed brown atrophy; the aorta marked endarteritis, but without calcification. Aortic and mitral segments thickened. The large vessels of the abdomen showed moderate endarteritis. Lungs showed emphysema and cavitation in the apices, apparently tuberculous, but no longer active. The liver was fatty. The kidneys showed marked chronic interstitial and fatty, with parenchymatous changes. The renal arteries showed marked endarteritis. The bladder showed ulcerative cystitis.

The second to the sixth inclusive posterior spinal processes were bifid.

The vessels of the spinal canal showed extreme congestion especially in lower dorsal and lumbar regions. They showed moderate sclerosis. The spinal dura was normal. The first evidence of spinal disease was found at the first dorsal level, manifested by a small area of softening in the left anterior horn. At the level of the fifth dorsal segment the entire gray matter was soft and infiltrated with blood. In the mid-dorsal region the anterior horns appeared to be almost universally softened. In the lower lumbar region the softening had so generally involved all structures as to convert it into an unrecognizable mass.

The direct cause of death was sepsis originating from a large trophic ulcer over the sacrum or perhaps from the cystitis.

Case IV.—The patient entered the fourth medical service of Bellevue Hospital unable to give any personal history, and the few details obtained were given by her neighbors.

She was twenty-five years old, supposed to be in good health, and no previous illnesses were known of. She was known among her neighbors as a hard drinker and as of liberal morals. Two days previous to her entrance to the hospital she complained of some headache. On the succeeding day she still suffered, and during the morning drank a quart of whisky. In the afternoon she felt considerably better, but at about 6 P.M., while at stool, she noticed that her feet and hands were becoming numb. She was taken to the hospital on the next day. Absolute anesthesia and paralysis of the lower extremities, abdomen, and, to a lesser degree, of the thorax also, together with slight involvement of the upper extremities. The paralysis and anesthesia rapidly extended upward, and she died before her physical examination had been completed.

The autopsy was performed early the next day, the body having meantime been preserved by efficient cold storage. The external examination of the body revealed nothing except that the pupils were irregularly dilated. The condition of the body indicated involuntary evacuations of feces and urine.

Examination of the spinal canal was only permitted. A large amount of clear colorless cerebrospinal fluid was found, and the vessels of the channel, including those of the spinal dura, were found much congested and considerably sclerosed.

Gross examination showed involvement of the spinal gray matter alone. It was found to be the seat of an acute hemorrhage, softening extending from the cervical levels downward. Apparently the hemorrhage had progressed along, and largely, if not entirely, through the medium of the ventricle of the spinal cord.

One factor which all of these instances possess in common is that in each definite disease of the spinal bloodvessels was present.

In Cases I and IV syphilis is thus, in all probability, the chief determining factor, and in Case II age is apparently of most definite bearing, though this example also presents the only instance of a possible traumatic factor. Case III represents as the most likely agent concerned in the production of arterial disease, the excessive use of tobacco and alcoholism, which is also a factor in Cases I and IV.

These facts are in direct contraversion to the commonly accepted text-book statement. Thus Church and Peterson state that the changes in the arterial coats are of lesser importance in spinal hemorrhage, and E. Farquhar Buzzard, in Osler's *System* (vol. vii, p. 274), makes the statement that sclerotic changes in the vessels do not appear to very generally determine the lesion. The author is impressed from the statements made by most authors that cases have not been adequately investigated as to this possibility, which is of acknowledged importance in every other type of hemorrhage. It would appear to the writer that spinal hemorrhage in this characteristic in no way differs from hemorrhage elsewhere, and that it is especially similar to brain hemorrhage.

The statement is made by some authors that spinal hemorrhage customarily takes place in a previously existing area of softening. Though it is impossible to absolutely exclude this possibility, at least it is highly improbable, for in the cases thus reported any lesion of sufficient size to favor such a condition could not long exist in so limited and vital a territory as the spinal cord without producing symptoms of an obvious character. Such signs are entirely wanting in these cases. Eichorst, in 1874, first recognized that central hemorrhage might take place in previously normal cords, and in all probability this is the rule and not the exception.

As to the immediately determining factor, Buzzard states the most frequent factors to be trauma or strain, and Church and Peterson seem impressed with the idea that arterial pressure and direct cardiac impulse which play so important a role in brain hemorrhage are absent or unimportant in spinal hemorrhage. The writer's impressions from a study of the literature of the subject and from these four cases is that precisely similar factors are at work here as in cerebral hemorrhage, but obviously under conditions varying

from those dominant in cerebral hemorrhage. Thus, for example, we find cerebral hemorrhage occurring most frequently in conditions of mental strain, and in all except Case II of this group a definite factor of primary spinal stress was present. Straining at stool was apparently the immediate cause in two of my cases. Oppenheim cites a case occurring during the manual of arms drill. Gowers mentions a case occurring after excessive coitus, and so on.

Traumatism is mentioned by most authors as an important factor in the cause of spinal hemorrhages. One should exclude in this review those instances in which actual crushing of the cord occurs, since the lesion in true hematomyelia is one of gray matter hemorrhage only and is quite distinct from that which might occur in direct spinal injuries. In only one of these four instances is a possible traumatic factor concerned, that is in Case II. It must be noted that no evidence of direct spinal injury was found postmortem in this instance, and it is possible that the hemorrhage caused the fall, resulting in the accident, and not *vice versa*.

As is always the case in hematomyelia, the blood extravasation has extended along and about the spinal ventricle, and in no instance has extended out into the white matter. This is doubtless due, as all students of the subject have conceded, to purely mechanical factors.

In conclusion, as a result of the study of these instances, one is impelled to the idea that contrary to the prevaling view, arterial changes as a predisposing factor are present in hematomyelia, and that the dominant agent in the immediate determination of the hemorrhage is that of strain, involving spinal activity or tension.

THE PRESENT STATUS AND THE FUTURE OF HYGIENE OR PUBLIC HEALTH IN AMERICA

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During the past few years an increasing and now insistent demand has been heard in this country for better facilities for the training of public health officials. This demand has come from members of the medical profession, chiefly those engaged in official positions as officers or commissioners of health for cities and states, from sanitary engineers, and from various philanthropic societies whose aim is the betterment of social conditions among the poor in our great cities and in our rural communities. With the last this demand is associated with a demand for more enlightened instruction for the general public in matters affecting their health. At this time when these various desires are but an index of the awakening of interest throughout this country in that branch of science known as hygiene or public health, it becomes a matter of vital necessity for those of us who are working in this field to clearly formulate the underlying principles of this science, its scope and its needs, and present them to the public and especially to those who hold the fate of our great institutions of learning in their grasp and under their direction.

Hygiene in Germany and Austria. Despite the fact that an American-born scientist, Count Rumford, of Munich (Benjamin Thompson, of Concord and Boston), was the first to inaugurate and carry out a comprehensive movement for the betterment of living conditions among the very poor, during the course of which he made a most accurate and painstaking study of the many factors leading to poverty and ill-health and suggested remedies for them,

the modern conception of hygiene was given the continent of Europe by Max von Pettenkofer, the first professor of hygiene in Munich and, indeed, the first professor of hygiene in any German university. A pupil of Liebig and Voit and a well-trained chemist, Pettenkofer first served as professor of chemistry in Munich, but in 1865 transferred his activities to the science of hygiene, a professorship of which was established for him in this Bavarian institution. More than any other man of his time, Pettenkofer saw clearly the prevailing chaos in the facts and theories relating to the science of health and especially in regard to the infectious diseases. At that time epidemic after epidemic of typhoid fever devasted the population of such cities as Munich and Vienna, Asiatic cholera was always knocking at the doors of central Europe and frequently obtained admission, while other zymotic diseases spread like wildfire from person to person when once started in a community. The laws passed to control these epidemics were ineffective and the mortality from disease extremely high. The single exception to the prevailing helplessness was the Jennerian vaccination which had placed smallpox in the sphere of controllable diseases. Pettenkofer not only realized the inadequacy of the methods employed to limit the spread of disease, but he also saw that the fundamental difficulty lay in the ignorance of the medical profession in regard to the mode of transmission of infections from one individual to another. In this great crisis, for such indeed he felt it to be, Pettenkofer raised a powerful voice and demanded that the various facts relating to disease "en masse" should be thoroughly studied by experts just as the symptoms and pathology of individual cases were being studied by experts, that after the fundamental fact had been observed on a broad basis, theories to explain these facts should be formulated and submitted to the rigid test of experiment, to the end that proper conclusions from fact, theory and experiment might be drawn and measures in accord with these conclusions be carried out. In other words, Pettenkofer demanded that the empiricism of hygiene should be converted into a science. To accomplish this he further insisted that departments of hygiene be established in the various universities, that proper equipment be provided to gather the data and test the theories of hygiene, and

that trained scientists be given the opportunity of carrying out this work. The widespread agitation coming from the movement originated by von Pettenkofer resulted in the establishment of a department of hygiene in the University of Munich, the selection of von Pettenkofer as professor and the construction of a hygienic institute. This institute founded in 1865 still stands, I believe, although plans for a new building upon somewhat more modern lines have now been completed.

From this brief résumé it may be seen that Pettenkofer was really the founder of modern hygiene, at least in so far as the German-speaking races were concerned. He occupies indeed the same position in regard to hygiene that Virchow does in pathology.[1] The radical movement in hygiene fathered by him made a profound impression upon Europe, especially upon Germany and Austria. Professorships were established in the leading medical schools, first in Bavaria and then in other parts of the German empire, thoroughly trained men were put in charge of the administration of sanitary laws and the attempt made to limit the spread of the infectious diseases by scientific methods. The new knowledge acquired by Pettenkofer and his pupils, and the laws promulgated at their suggestion soon began to have a definite influence upon the mortality returns. In the city of Munich, for instance, the sewage system was reconstructed and proper methods established for drawing off human and animal wastes, a new and pure supply of drinking water was obtained, old, ill-constructed houses were pulled down and air and sunshine admitted to the darkest sections of the city. A special corps of sanitary police was instituted, the members of which were given extraordinary powers so that they could visit every quarter of the city, and enter every dwelling to enforce the execution of the new sanitary laws. As a result of these

[1] An interesting analogy is also evident in the domain of therapeutics. In this science Schmiedeberg, a pupil of Bucheim, who founded the first laboratory for the scientific study of drugs in Dorpat, realized the inadequacy of the existing knowledge of the composition and the action of the various remedies employed by the medical profession largely on an empirical basis. He demanded that the medical profession turn from the clinic to the laboratory, study the chemical composition of drugs, determine their action by animal experimentation and endeavor to explain this action by the facts and theories of physiology. Under the leadership of Schmiedeberg the new science of pharmacology was established to take the place of the older science of therapeutics.

sweeping changes the mortality from zymotic diseases fell rapidly in Munich and typhoid fever practically disappeared. In Vienna also, where Gruber, a pupil of von Pettenkofer, became professor of hygiene in the university, a similar change took place. Here was a city built within narrow walls, the population crowded together in unsanitary quarters with a water supply from surface wells sunk in a sewage-permeated soil. Sweeping reforms were instituted in this old medieval town, a new method of sewage disposal established, a new water supply obtained and in a surprisingly short time the typhoid mortality was cut in two. Whereas in 1874 it had been 15–16 per thousand, by the end of two years it had fallen to 7-8 per thousand and subsequently steadily diminished.

Under the stimulus of von Pettenkofer the new science of hygiene developed rapidly and from his institute in Munich his pupils passed first to one and then to another of the European universities as the chairs of hygiene were founded. Thus Buchner became associated with hygiene in Munich, Gruber went to Vienna, von Fodor to Budapest, Flügge to Göttingen (later to Breslau), Hofman to Leipzig, Lehmann to Würzburg, Rubner to Marburg, Pfeiffer to Rostock and Prausnitz to Gratz. The science of hygiene was established upon a firm basis and it is not too much to say that the movement inaugurated by von Pettenkofer was one of the most important movements in the science of medicine of the nineteenth century.

The Munich school of hygiene was developed in the days before modern bacteriology was dreamed of however, the etiological agents of disease were unknown and much of the work of the great investigators had to be carried out upon a hypothetical basis. This is best shown by the famous $x\ y\ z$ hypothesis of von Pettenkofer by means of which he attempted to explain the spread of the diseases in which the intestinal tract is involved, typhoid fever, cholera and dysentery, the so-called diseases of the soil, or Bodenkrankheiten. The kernel of this hypothesis lay in von Pettenkofer's belief that the unknown etiological agents of these diseases must undergo a process of modification or ripening in the soil before they are in a condition to produce the disease in other individuals. With the rise of the new science of bacteriology as the result of the

wonderful and brilliant investigations of Robert Koch and his immediate pupils, especially the discovery of the responsible parasites of anthrax, tuberculosis, Asiatic cholera and typhoid fever, the Munich school of hygiene received a staggering blow. Here were the hypothetical etiological agents of disease capable of demonstration under the microscope and of cultivation in the laboratory. Why waste one's time indeed in arguing about an unknown factor when this factor had been discovered and identified and the facts relating to it could be accurately studied? This was especially the case with Asiatic cholera where methods had been devised for the accurate bacteriological examination of suspected cases by the use of which an almost absolute diagnosis could be made in forty-eight hours and the infected individuals quarantined, the simplest possible method of preventing the introduction of this fearful scourge into any community. But the Munich school of hygiene died hard and in the long and somewhat bitter controversy between the old and the new, between Pettenkofer and his pupils and Koch and his, most important facts bearing upon the etiology of the infectious diseases were established. Gradually, however, the newer and more correct theories of the modern bacteriologists supplanted the older and often incorrect theories of the Pettenkofer school and in 1885 Koch became professor of hygiene and bacteriology in the University of Berlin. This set the pace and within the next few years the various professorships of hygiene as they became vacant were filled by the appointment of men trained in the modern bacteriological technique. Thus Gaffky, the discoverer of the typhoid bacillus, went to Giessen, Loeffler, the co-discoverer with Klebs of the diphtheria bacillus, to Griefswald, Hueppe to Prague, von Behring to Halle and Marburg, Carl Fraenkel to Marburg and Halle and Gärtner to Jena. At the same time hygienic institutes corresponding somewhat to our municipal health laboratories were founded in many of the larger cities of Germany and Austria to provide for the accurate bacteriological diagnosis of the infectious diseases. The largest and best-equipped of such institutes is probably that of Professor Dunbar in Hamburg, one of the few American-born scientists to make his career in Germany. A more recent institute of the same

general character is that of the city of Frankfurt a. M. under the able direction of Professor Neisser. With the single exception of the laboratories of the City of New York there are no institutions in America which are founded upon quite the same broad combination of routine work and advanced research as are these.

As a result of the various factors operating to develop the modern science of hygiene in Europe we find that this subject is now firmly established in all the German and Austrian universities. It is a principal or major subject in every medical school and there is an "ordentlich Professor" of hygiene in every university where medicine is taught. Every student of medicine must pass a rigid examination in hygiene before he can obtain his degree and before he can practise his profession. As was to be expected from the somewhat diverse lines of development hygiene has taken we find men of various tendencies occupying the professorships. On the one hand Flügge and Gruber represent the older or Munich school at Berlin and Munich, both trained in the Pettenkofer methods but both greatly influenced in their thought and work by the newer bacteriology of Koch. In Berlin also before the appointment of Professor Flügge, hygiene was brilliantly represented by another product of the Munich school, Professor Rubner, now professor of physiology. On the other hand, many other chairs of hygiene in Europe are held by the bacteriologists, as by Kruse in Königsberg, by Fischer in Kiehl, by Uhlenhuth in Strassburg, by Kolle in Berne, by Schottelius in Freiburg i. B., and by Neumann in Giessen. At the same time hygiene is taught in Vienna by Shattenfroh and Grassberger who clearly unite the two schools, while in Budapest von Lieberman is associated with von Fodor, and may be said to approach the subject more from the standpoint of the physicist.

Despite the great diversity in training of the various hygienists in Germany and Austria, the subjects they teach and study are much the same in the different universities, approached necessarily, however, from different viewpoints. The fundamental principles of hygiene as applied to vital statistics, heating, lighting, ventilation, clothing, disinfection, sanitation, water and milk supplies, sewage disposal, nutrition and food values are taught to all medical

students, while special emphasis is laid upon demonstrations which show the mode of transmission of the infectious diseases. Lecture courses in theoretical hygiene are compulsory, laboratory courses in practical hygiene are attended by the majority and all students who are candidates for degrees in medicine must pass a rigid examination in hygiene before graduation. At the same time special courses in hygiene are offered in all the hygienic institutes. They cover a variety of subjects and include such topics as school hygiene, mental hygiene, the hygiene of inheritance, nutrition and systematic instruction in the principles of infection and immunity. Finally elementary bacteriology is taught the medical students in many of the hygienic institutes, which in a few instances provide facilities for the cities where the universities are located for diagnostic work in connection with the infectious diseases. No matter how seemingly diverse the subjects or how varied the interests of the many workers in the field, hygiene is a distinct scientific entity in central Europe today, the object of whose teaching is the demonstration of all the available facts and theories relating to disease in bulk as distinguished from individual cases of disease.

Hygiene or Public Health in Great Britian. During the period which saw the establishment of hygiene on a modern basis in Germany and Austria, the same science was being developed in England under the name "public health." In Great Britain the system of local control of public affairs had spread more widely than in any of the continental countries, in consequence of which the local authorities were enabled to dictate their own mode of government. Local organizations were formed to control all matters relating to the health of the community and the system of local government boards with their peculiar privileges and responsibilities has resulted. This system represents indeed Great Britain's especial contribution to hygiene in the last century, and the years 1847 when medical officers of health were first appointed, 1848 when they were required to be qualified medical practitioners (Public Health Act), 1855 when every vestry and district board in London was required to appoint one or more medical officers of health, and 1872 when the new Public Health Act forced every sanitary authority outside of London to appoint

a medical officer of health, formed the especial landmarks in this chronological development. Long before 1847, however, English physicians had devoted time, energy and thought to the problems of hygiene, and the names dear to the heart of every Anglo-Saxon are scattered over the pages of English medical history. Thus in 1720 Dr. Richard Mead, the physician to St. Thomas Hospital, published his "Short Discourse Concerning Pestilential Contagion and the Methods to be Used to Prevent It," a book which went through seven editions in its first year of life. In 1764 appeared Dr. John Pringle's work on "Diseases of the Army," which was destined to revolutionize sanitary conditions in jails and hospitals as well as in military camps, while the same service was rendered the navy by Dr. James Lind's publication entitled, "On the Means of Preserving the Health of Seamen," soon followed by a series of essays concerning the health of the Royal Navy, on "Fevers and Infection" and on "Jail Distemper." Dr. Gilbert Blane's "Observations on the Diseases of Seamen" appeared in 1785, and in 1796, when Blane was serving as chief officer of the Naval Medical Board under the admiralty, lemon-juice was added to the diet of the seamen and scurvy ceased to rage. Dr. George Baker, in 1767, elucidated the etiology of "colic and palsy" in Devonshire and by his demonstration that this was lead poisoning pure and simple first put the study of industrial diseases upon a scientific foundation. More important than any other single discovery, however, and more beneficial from the world-wide campaign it inaugurated against smallpox, stands of course Jenner's discovery of cowpox vaccination in 1798.

In the century from 1738 to 1838 England saw its great rejuvenation manifest in its acute religious revivals, its political emancipation, the social liberation of its lowest classes and the destruction of class privilege, the extinction of slavery, the improvement of agriculture, the extension of trade and commerce and the organization of its industries on a firm basis. During all this time great movements were usually associated with great men, and the names of John and Charles Wesley, George Whitfield, Adam Smith, Jeremy Bentham, John Howard and William Wilberforce will always be held in affectionate reverence by those

who are alive to the ills of mankind and who love their fellowmen. By 1838 England had been thoroughly purged of many of its ills, and when ten years later the first systematic efforts to regulate the sanitary affairs of London began the government found a population no longer hostile to sanitary reform. During most of the subsequent period one figure looms up persistently in public health in the United Kingdom, Sir John Simon, who bears much the same relationship to English hygiene that Pettenkofer does to German, and who was fortunately also spared till close to the end of the last century.

As a result of the Public Health Act of 1872 it became apparent that the supply of men trained in sanitary science to occupy positions as public health officers was inadequate and the University of Cambridge set about the task of remedying the difficulty. For this purpose it established the system of examining qualified medical practitioners in the principles of hygiene and granting diplomas to those who satisfactorily passed the examination. In this work the great hygienist Parkes was the leading spirit. The diploma granted came to be known as the D.P.H. or Diploma of Public Health, the holders of such diplomas having a distinct advantage over their competitors when they applied for the coveted positions with the various local government boards. The great advantage to any community in having its medical officer of health a trained sanitarian was soon apparent and in 1892 an act was passed which required every medical officer of health to have a diploma of public health in every district of 50,000 inhabitants or to have served as health officer before the passage of the act. Thus a medical officer of health in Great Britain is not only a qualified practitioner of medicine but is a trained sanitarian as well.

The example set by Cambridge in granting the D. P. H. was soon followed by other universities in the United Kingdom, and at the present time this or a similar degree with the same general purpose is granted in sixteen of the universities in Great Britain as well as by the Conjoint Board of the Royal Colleges of Physicians and Surgeons in England, in Ireland and in Scotland. At the same time the various universities offer courses of instruction in hygiene or public health which qualify men to pass the examina-

tions. In general the work required of a candidate covers nine calendar months, thus corresponding to a year's postgraduate work in America. During this period the candidate spends four months in studying the principles of sanitary science in their application to public health problems, "air, water, soil, sewage, food, climatology, bacteriology, parasitology and the general pathology of diseases of animals transmissible to man, etc." (See Nuttall.) Following this he receives instruction in sanitary engineering, food inspection, epidemiology, occupational hygiene, vital statistics and public health laws. Finally during six of the nine months the student must study public health administration under a qualified medical officer of health and during three months must attend a hospital for infectious diseases and acquire training in diagnosis and in preventive methods. In addition to the men who expect to enter upon an administrative career in public health in Great Britain and who are now required to obtain this diploma, many medical graduates take the D.P.H. as a post-graduate degree corresponding somewhat to our Master of Arts and a large number of the most eminent scientists in the medical profession there are holders of diplomas in public health. Whatever else may be said of the public health instruction in Great Britain, and however true some of the criticisms leveled at it may be, it must be admitted that this system has resulted in an enlightened control of sanitary measures by competent authorities which is not surpassed by any other country in the world. How well this system fits into the general political and governmental systems of Great Britain is shown by a glance at their mortality returns, in which a death from typhoid fever is so rare as to be an occasion for comment, or in a study of the distribution of rabies, which seldom or never appears in the British Isles. The English conception of public health differs essentially from the German conception of hygiene, however, and while differences are difficult to formulate, it may be said in general that in England attention is focused upon the administrative side of the subject, while in Germany the emphasis is laid upon the theoretical or purely scientific aspects of the science. This does not mean that in Great Britain the scientific side of public health has been neglected or that in Germany the practical side of hygiene

has been forgotten. It is nevertheless true that the modern conception of public health has been furnished the world by Great Britain just as the modern conception of hygiene has been developed in Germany and Austria and that there are certain differences between the two conceptions.

The English notion of public health prevails in Great Britain's colonies, and some years ago the late Wyatt Johnston, of Montreal, established a systematic course of instruction in this branch in McGill University which was the first institution in America to grant a diploma of public health.

Hygiene or Public Health in France. In France also from early times thoughful medical men and government officials were deeply concerned with the health of the people and alive to the necessity of studying and reforming sanitary conditions. On July 6, 1802, Dubois, prefect of police in the City of Paris, founded the Council of Health or Conseil de Salubrité with four members, Deyeux, Parmentier, Huzard and Cadet-Gassicourt. The organization of this body was modified by subsequent decrees in 1810 and in 1815, and similar bodies were formed in Nantes and Bordeaux in 1815, in Lyons in 1822, in Marseilles in 1825, in Lisle (Lille) in 1828, and in Rouen in 1831. In 1848, the year that saw the first Public Health Act of Great Britain, the Conseil d'Etat passed an ordinance for general health regulation throughout France. Since that time the administration of health laws has been on a firm and scientific basis in France and many medical men of prominence, like Thouret, Leroux and Dupuytren, have been members of the various councils of health. In general the administration of health or sanitary laws is in the hands of the department of police (law, etc.), the Conseil de Salubrité being entirely a consultative body. Its decisions have the practical force of laws, however, and are seldom reversed. At irregular intervals voluminous reports are issued, relating to health, salubrity, and industry. The regulations under the caption Health relate to food and its adulterations, poisonous substances found in it, kind of vessels used in its manufacture, etc. Under Salubrity is considered the regulation of anatomical theatres, barracks for soldiers, public baths, street fountains, water supplies, factories, prisons, markets, and disposal

of filth. Finally Industry covers the bituminous trades, manufacture of candles, slaughter houses, powder mills, white lead factories, and all places where poisonous gases are liberated. From time to time the old regulations are modified to meet the needs of modern civilization and new regulations promulgated. The wonderful sewerage system of Paris and the beautiful gardens for sewage disposal on the banks of the Seine a few miles below Paris are lasting monuments to the genius of the French hygienists, and the leading positions which French authorities occupy in the scientific development of quarantine testify to their soundness and versatility. French hygiene or public health, however, has been especially influenced in its later development by Pasteur and the various institutes named after him and has, to a considerable extent, developed the idea of preventive medicine. The Pasteur Institute in Paris, originally designed for the study of rabies and the preparation of anti-rabic inoculations, soon took on the character of a general bacteriological and hygienic institute in which the problems of all the infectious diseases were investigated. The other Pasteur Institutes in France and her colonies have also been modeled on the same general plan. Hygiene likewise is an important part of the medical curriculum and a number of standard publications are devoted to it.

Hygiene or Public Health in America. When we now turn to the consideration of hygiene or public health in America, it is at once evident that the greatest confusion of ideas prevails concerning the subject. Authorities are not agreed upon even the fundamental definition of the science, the development of which has been both sporadic and limited. It is high time indeed that we should have some sort of free discussion of the whole matter, particularly as to the best lines for the future growth of the beginnings already made. Certain fundamental facts stand out clearly. The most important of these is that municipal and state authorities have for years recognized the needs of safeguarding the public health and have established various institutions for this purpose, especially our city and state departments of health. Thus as far back as 1856 our state boards of health were well organized and held an important conference in Philadelphia to deal with the

vexing question of yellow fever which appeared at Bay Ridge the previous year. The national government has lagged far behind other countries in public health matters, however, and a national department of health, so vital to the interests and happiness of every citizen of the United States, has thus far failed of establishment. The abortive attempt made to bring about this much needed reform, in the early eighties, led to the foundation of such a department, which led a precarious existence of only two years. Fortunately the Marine Hospital Service has gradually been able to take up many of the duties of a national department of health and has now become in fact and in name a Public Health Service.

In our universities and in our medical schools, while hygiene was early recognized as a major subject by many of our leaders in medical education, this feeling was by no means widespread. Nevertheless important beginnings were attempted and in some instances splendid results followed. As early as 1865, the year von Pettenkofer became professor of hygiene in Munich, the medical college of the New York Infirmary for Women and Children made hygiene and public sanitation a compulsory part of its curriculum. Even before this the Woman's Medical College of Pennsylvania had taught hygiene in association with physiology. The University of Michigan when its medical department was founded in 1850 taught the principles of the sanitary analysis of drinking water to its students, in the early seventies lectures on hygiene were given to both medical and literary students by the late Dr. Corydon Ford, and in 1876 a course of lectures was given on this subject by the present professor of hygiene there. In 1887 the state legislature made an appropriation for a hygienic laboratory which was formally opened in the session of 1887–88. In Western Reserve, in Cleveland, state medicine and hygiene were taught as early as 1881, sometimes in association with pathology and again in connection with clinical subjects. In Harvard lectures on hygiene were given in 1876, and the present department of preventive medicine was established later as a department of hygiene with the late Dr. Harrington as director. In 1892 the institute of hygiene of the University of Pennsylvania was established upon a broad foundation with the gifted Dr. Billings in

charge and in this institute we see most clearly the influence of the Munich school of hygiene upon medical thought in America. Foundations of hygiene were likewise provided for in many other medical schools, such as the University of California and Cooper Medical School in San Francisco. With the exception of Michigan, Pennsylvania and Harvard, however, the hygiene which was taught in America was presented either by practising physicians or by health officers whose time was largely occupied by administrative duties and who gave brief and in general unscientific lectures upon public health topics to medical students. The excellent example set by three of our leading medical schools was not followed, the science of hygiene failed to develop generally and in many instances the older foundations of hygiene were abandoned to make room for subjects regarded as of greater necessity in the medical curriculum. Thus the department of hygiene in Cooper Medical School, now Leland Stanford, gave way to a department of bacteriology. Recently, however, Western Reserve has reorganized its work in hygiene and has appointed a full-time professor in this branch, a similar change has taken place in Yale and the relatively new University of Chicago has also established such a department. With all this hygiene as a major subject, with a trained scientist giving up his entire time to teaching its principles and studying its problems, exists in but six of our thirty-eight medical schools today. What a pitiful showing this makes in comparison with Germany and Austro-Hungary, where all the twenty-two universities where medicine is taught have their hygienic institutes, or with Great Britain, where every graduate in medicine must follow courses in public health and pass examinations in it. I do not mean that many of our medical schools are not making a determined effort to develop the subject of hygiene or that instruction in it is entirely lacking. Indeed, excellent courses in public health are given in both Minnesota and Indiana. In the three larger medical schools in New York City hygiene or public health has now become compulsory. At Johns Hopkins, too, the faculty has long recognized the necessity of further development along this line and the beginnings, small though they are, have now been made. I merely wish to point out and emphasize that the science of hygiene, one of the

most important parts of a medical curriculum, has never reached the same development as an independent subject which has long been attained in Europe, and which has already been reached in America by the scientific branches of medicine, anatomy, physiology, chemistry, pathology and pharmacology, or by the clinical, surgery, medicine and gynecology and obstetrics.

In the same way and possibly as the result of the same influences, hygiene plays but an unimportant part in our state examinations for licensing practitioners of medicine. In but a few states is there a separate examination in hygiene and in some the subject is not even mentioned. Yet there is probably no field in which medical men need training more than in hygiene and in no line of work will his efforts be more beneficial or more appreciated by the community than in the prevention of the spread of infectious diseases by the application of the sound principles of sanitation. The medical profession of America is neither indifferent to the great problems of preventive medicine nor ignorant of its principles however. The long and honorable career of the American Public Health Association and the more recent development of the Section of Hygiene and Preventive Medicine of the American Medical Association testify to the contrary. The indifference to hygiene as a science lies in our universities and in our medical schools and the responsibility for the failure of its development rests clearly upon them.

Present Needs. The question now rises as to the especial needs of hygiene, and the conditions which must be met in order that it shall develop. We may best consider this under three divisions.

There is first a definite need and even a necessity for the training of medical students in the science of health, whether the science be labeled hygiene, public health or preventive medicine. Every man who graduates from a medical school should be taught, some time during his course, the underlying principles of hygiene. He should know what the word ventilation means, for instance, something about clothing, the kinds of exercise suitable for different individuals, the values of foods, how a good water supply differs from a poor one, what good milk is, how a city should dispose of its sewage. Especially should he be taught the mode of transmission

of the infectious diseases and the methods of their prevention. This knowledge the well-trained physician of the future must have, not merely that he may advise his patients properly and safeguard their health, but that he may play his part in the community where he lives and lift his voice on the right side concerning that branch of city and state government which most concerns him, the department of health, too often alas merely a pawn in the hands of unscrupulous individuals to move as they see fit in the great game of politics. To accomplish this purpose, namely, the education of the physician, every medical school in this country should have its department or institute of hygiene in charge of a full-time man with a corps of trained assistants. It makes little difference whether the head of this department is a chemist, a bacteriologist or a physicist, since the problems of hygiene must be approached from various angles, but in the organization of the department provision must be made for teaching the subject with reference to chemistry, bacteriology, and physics. Didactic lectures in hygiene must be combined with laboratory exercises and the student must acquire first-hand knowledge of water and milk analysis, disinfection, sanitation, and especially the bacteriological diagnosis and the prophylaxis of the infectious diseases. In addition special courses should be offered in such topics as school hygiene, serum-therapy, nutrition and food valuations, etc. The research side should also play a large part in any department of hygiene. It is not sufficient to teach what we know at present about hygiene. The bounds of our knowledge must be constantly widened, new facts acquired and new theories tested.

The relationship of the department of hygiene to the medical school should also be made clear. It is essential that hygiene be presented as a distinct and independent science and not as a phase of bacteriology, or of chemistry, or of physics. How far the department of hygiene should engage in teaching the elementary principles of the sciences whose methods it uses is also an important question but chiefly as it affects bacteriology. This after all is a matter of merely academic interest. Bacteriology must always be taught medical students from the standpoint of the pathogenic bacteria. If the pathological laboratory has the facilities for teaching bac-

teriology and the staff have the training there is no reason why general bacteriology should not be taught with pathology. Nor is there any reason why bacteriology should not exist as a separate department in the medical school if funds are available for this purpose. At the same time there is no reason why general bacteriology should not be taught in the hygienic institute so long as it does not encroach upon the teaching of hygiene and provided the head of the department has received the proper training and understands the fundamental principles of infection and immunity. Above all it must be remembered that hygiene is a medical subject and a part of medicine. Its methods are the methods of medicine and have been developed in the medical departments of the European and American universities. Hygiene must therefore always be taught medical students from the medical point of view by medical men.

The second great need in this country is for better facilities for the training of public health officers. The awakening of the public conscience to the necessity of removing health questions from the domain of politics has resulted in the reorganization of many of our municipal and state departments of health while the excellent achievements of others have given them greater responsibilities and increased facilities for carrying out their work. The system of "county health officers" in which employees of the state department of health are empowered to assume local duties either in coöperation with the local authorities or superseding them has now been adopted in two States and marks a signal advance in health legislation. This is an example, indeed, likely to be followed by a number of States as time goes on. This change in health administration has created a distinct demand for specialists in public health and the medical departments of our universities must now see to it that the men who take up public health as a career are given the opportunities of fitting themselves properly in the science of hygiene or public health. This can probably best be accomplished by organizing courses leading up to the Diploma of Public Health or some similar degree, the possession of which will guarantee that the holder has received expert instruction which will qualify him to act intellignetly as an officer of health. Already

three of our best medical schools have organized such courses and other universities are contemplating similar enterprises. It is not enough that this or that school shall establish departments for the training of health officials. This movement is one which vitally concerns the physicians of this country and is likely to have an important influence upon the development of American medicine. The medical profession must demand that our health officers be properly trained, that the Diploma of Public Health shall not be awarded to any sort of individual regardless of his preliminary training to be used merely as a lever to help him to acquire a position. There must be some sort of standardization of the courses leading up to the degree and particularly must there be some agreement as to their length and the amount of time which must be passed in preparation for the examinations. Above all, American physicians must remember that the health officer, be he county, city or state, has a distinct function, the intelligent exercise of which requires a medical training. It is not enough that our garbage be disposed of, that our drinking water be chlorinated or filtered, the bacteria in milk be counted or the births and deaths of a community be registered, important as these activities may be. It is far more important that the unsuspected and unreported case of typhoid fever or septic sore throat be ferreted out, the typhoid or diphtheria carrier be recognized, the first case of smallpox be differentiated from chickenpox and that the correct diagnosis of the obscure cases of meningitis or some of the exanthemata be established. It is after all in the great field of the preventable diseases of infectious nature that the health officers will do the most work and bear the heaviest responsibilities. Thus while an engineer or a half-trained medical man who has specialized in public health may satisfactorily perform the functions of a health officer in certain particulars it is difficult to see how he can perform the most important. This is a particularly grave problem in maritime cities where the danger of bubonic plague is constantly increasing or where a case of yellow fever may slip in almost any time. It is an important question therefore whether the American medical profession shall permit to develop unchallenged that movement now grown so powerful in this country whereby non-

medical men are elevated to positions of authority and responsibility in public health matters, which after all are medical matters. Without doubt many non-medical men may become expert health officers and discharge their duties to the communities which they serve in an intelligent manner. Can they be trusted in a crisis, however, and are we willing as physicians that a practise so fraught with danger be continued?

Finally, how can we educate the great mass of people in this country who are engaging in all sorts of philanthropic enterprises which verge on medicine, or which require some medical advice and assistance if all this work is to be prosecuted intelligently? These individuals are constantly turning to the medical profession for the solutions of knotty, difficult problems and indeed in no time in the history of this country have physicians had greater opportunities of directing broad, comprehensive charitable movements in the proper direction so that great sums of money shall be intelligently used for useful and beneficial objects. This education of the people in matters affecting their health can probably best be given in a museum of hygiene where models of all sorts of apparatus, collections of charts and statistical materials can be made available for study, where public lectures can be given on health topics, where experts in various lines can be consulted, where commissions can be formed for the investigation of special problems of public health. Such a museum would become a great centre for education in hygiene and public health and prove of incalculable benefit to the community in which it might happen to be located.

The question as to which of these three needs should first be satisfied is not easy to answer and the answer will also vary according to the individual point of view of those of us who study the problems. They are here presented in what seems to me to be the logical arrangement. If possible let us first educate our medical students, then our officers of health, then the public. Should the order be changed, however, no great harm will result. Should this country be so fortunate as to see schools of hygiene attached to the medical departments of our universities properly endowed

and aiming to satisfy all three needs, then indeed shall we be fortunate beyond the wildest dreams of the most enthusiastic student of the subject.

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DISCUSSION

Dr. M. J. Rosenau: I wish to express my appreciation of Dr. Ford's paper. The development of the science of public medicine may be divided into three stages:

1. Public hygiene: This began with the teachings of Pettenkofer, who is properly regarded as the father of modern hygiene. Pettenkofer's school dealt primarily with water supplies, disposal of sewage, draining of the soil, and care of the environment. It had a misconception of the etiology of disease and largely disregarded the personal element. The results of sanitation, as advocated by Pettenkofer, took care of certain diseases such as typhoid fever, cholera, dysentery, but failed to influence others. Beginning with the teachings of Koch, there came a second stage namely,

2. Preventive medicine: This second stage in public health work was the natural development resulting from the discovery of the causes of disease and their modes of transmission. The most brilliant results were in the field of diseases spread by insects. Good results were also had through vaccines and serums, as well as in tuberculosis and other communicable infections, spread by contact.

3. Personal hygiene: It was soon learned that many infections cannot be controlled through public means, but depend largely upon the individual. As an instance of this class, we have syphilis and gonorrhea. Effective personal hygiene depends not only upon self-control, but also upon education. The diffusion of knowledge has therefore become one of the important foundation stones in improving public health.

The need of trained public health officials must be met by special schools. Public health work has become a separate profession. In Boston an effort has been made along this line by establishing the School for Health Officers, conducted by Harvard University and the Massachusetts Institute of Technology, acting in coöperation. The medical faculty of the Harvard Medical School also offers courses leading to the degree of Doctor of Public Health.

Dr. John F. Anderson: The paper by Dr. Ford is timely and sets forth plainly the present status of hygiene in the United States as compared

with certain foreign countries. There is one point in connection with the public health movement to which I would like to refer and that is in regard to the efficiency of the local health officer. There can be no doubt that the crux of the whole public health problem is the efficiency of the local health officer, whether he be municipal or county. It seems to me that it is a matter well worthy of those universities which have established courses in public health to give this serious consideration, especially with a view to devising some means by which the local health officer may be put in the way of receiving a certain amount of instruction in public health matters.

Dr. George M. Kober: I am glad this matter has been presented as it has been in Dr. Ford's paper. Certainly we all agree that the highest aim of scientific medicine is the eradication of preventible diseases. But, in view of what has been said and in view of our common knowledge of prevalent conditions in this country, it is clearly our duty to take a greater interest in public health matters.

Great Britain deserves the credit for setting the pace over fifty years ago in the construction of great sanitary works, public health measures which have spread to all civilized countries and have resulted in great reduction of disease incidence. Such measures have not been neglected in this country, but much more remains to be done in the field of industrial hygiene. Last year there were 143,000 deaths from tuberculosis and over half of these were among industrial workers. It is believed that fully one-half of these lives could have been saved by the enactment and enforcement of strict factory laws for the protection of the workers from dust and fumes, the foes of industrial life. I hope every member will actively interest himself in this matter.

Dr. A. C. Abbott: I do not feel particularly pessimistic on the future of public health developments in this country. One has but to review the splendid progress in all the manifold departments of this work that has been made during the past twenty-five years, to be of my mind on the matter. In its modern development the subject is so comprehensive as to make compact or complete teaching difficult. Nevertheless there are a number of schools in this country which are now offering courses of instruction that seem to me to meet pretty well the needs of the case. This number will be increased as demand for trained men increases, and such demand is certainly growing.

What is needed now, in my judgment, is trained leaders who may serve, so to speak, as propagandists—who by educational methods will drive home to the people of all communities the fact that public hygiene is a special field of endeavor demanding the services of specially trained men; that the subject is not necessarily a medical one, but is as much social, economic and, to some extent, political.

There are in the United States a number of schools—particularly the State Universities—which have, in full running order, departments of instruction and investigation that might readily be coördinated in such a manner as to offer adequate instruction in the fundamental department of Public Hygiene. One cannot at this time say the last word as to just what such instruction should comprehend. Those of us engaged in the teaching of it feel ourselves in the experimental stage. That which seems satisfactory today, may be changed to meet the newer needs of tomorrow. But whatever the aims of teaching effort may be, it is my conviction that they fail, unless of sufficiently comprehensive nature to give to the student a clear, broad view of the many-sided problem that he will endeavor to solve.

RECENT APPLICATION OF CHEMOTHERAPY

WITH SPECIAL REFERENCE TO THE ACTION OF EMETIN UPON ENDAMEBA BUCCALIS, THE SPECIFIC CAUSE OF ALVEOLODENTAL PYORRHEA

By C. C. BASS, M.D.
NEW ORLEANS

The experiments of Vedder show conclusively that emetin kills certain cultural species of amebæ when they are exposed to its action. The species experimented with were killed by emetin in dilutions as high as one to 100,000 in a few hours. In order to determine whether this apparently specific amebacidal action may not be a general influence applicable to both protozoan and bacterial life, we recently added emetin hydrochlorid in various quantities to favorable culture media, which were then inoculated with certain species of common pathogenic bacteria. The bacteria employed were B. typhosus, B. coli, B. pestis, B. diphtheriæ, Staphylococcus aureus, Staphyloccus albus, and a strain of unidentified streptococci. Growth was prevented in all cases by emetin 1 to 100; it was less than in the controls in the presence of 1 to 500 in all cases; in the presence of emetin 1 to 5000 the test cultures showed approximately as many bacteria as the controls in all except in the case of *B. pestis* and *B. diphtheriæ*, in both of which there was definite antagonistic influence, but there was none in another test in which the proportion of emetin was 1 to 10,000. It would seem, therefore, from these observations that emetin not only is not lethal, but that it does not prevent the normal growth of these bacteria in solutions many times more concentrate than that in which it is lethal for certain cultural amebæ.

Roger[1] of the English Medical Service in India, with Vedder's observations as a basis, employed emetin hypodermically in the treatment of amebic dysentery with the most happy results. His observations have been followed by the most extensive employment of emetin in the treatment of dysentery throughout the world, until now it is a matter of general knowledge that most rapid and often almost marvelous effect upon the disease follows its use, and that these results are usually accompanied by temporary or permanent disappearance of the endamebæ present. The experiments with the drug *in vitro* and the clinical observations all go to show that emetin has specific amebacidal action, effective either in the test tube or in lesions in living tissues.

Endamebæ buccalis are present in the lesions of alveolodental pyorrhea. They are present in the very bottom of the pyorrhea pocket, where they move about over the inflamed suppurating area, and by their ameboid movements actually burrow into the inflamed tissues. Attention was recently directed to the probable etiological role of this parasite by Smith and Barrett.[2] One of the chief points of evidence shown of the pathogenicity of the parasite was the fact that rapid improvement followed the instillation of a solution of emetin into the pyorrhea lesions or pockets, and that this was coincident with the disappearance of the endamebæ. The strength of emetin solution employed was 1 to 200. This strength, as we have subsequently determined, is sufficient to interfere with the growth of bacterial life as well as with amebæ, and therefore the question could be raised whether, in this instance, the destruction of the endamebæ may not have been due to the action of such strong solutions of emetin upon all life, and not to any specific action upon the endamebæ.

We[3] have endeavored to shed further light upon the subject by administering emetin hydrochlorid hypodermically and noting the effect upon the endamebæ in the pyorrhea lesions in the mouth. These endamebæ are especially favorable for the study of the specific action of emetin because of the favorable location of the lesions for

[1] Brit. Med. Jour., June 22 and August 24, 1912; Therap. Gaz., xxxv, 837.
[2] Dental Cosmos, August, 1914.
[3] Bass and Johns, New Orleans Medical and Surgical Journal, November, 1914.

examination and observation of the behavior of the parasites. Up to the present time observations have been made upon a number of persons, and though there are certain unexpected difficulties in the way of exact determinations and conclusions, they have furnished valuable information, all of which indicates that emetin has specific amebacidal properties for Endameba buccalis, which are as definite, though possibly not as effectual, as it has for cultural and intestinal endamebæ. It was soon learned, however, that there was great difference in the effect of emetin given hypodermically upon the endamebæ in different people. In rare instances we have seen all demonstrable endamebæ disappear from all the pyorrhea pockets in quite advanced disease in twenty-four hours following a single dose of one-half grain of emetin hydrochlorid. In one such instance there was no reappearance of endamebæ for more than four months, showing that they had all been destroyed by the single dose of emetin. In the majority of cases, however, the demonstrable endamebæ disappear temporarily, at least, only after emetin hydrochlorid has been administered hypodermically in doses of one-half grain or more each day for a period of from three to six or more days. On the other hand there are a considerable number of persons in whom the endamebæ persist, in spite of prolonged daily hypodermic doses of emetin. It is interesting to note that the endamebæ seem to disappear from the smallest or least extensive lesions first in the cases of people having lesions which vary in extent. It would seem from this that possibly there may be some local condition which influences the action of emetin in different lesions, and possibly in those of different individuals.

It should be noted that this great variation in the effect of emetin administered hypodermically upon oral endamebæ in different individuals is exactly what occurs in the case of endamebæ in amebic dysentery. In spite of the generally favorable action there occasionally occur cases in which the drug seems to have only temporary or no effect. There is now a case of amebic dysentery in the medical service of the New Orleans Charity Hospital who has been given emetin sometimes for long periods of time during the past three years, but his endamebæ persist. During the early observation of the case the endamebæ would not be demonstrable after a few

days' treatment, sometimes for a month or more; but now they do not disappear in spite of large daily doses of emetin given hypodermically or intravenously over long periods of time. Though endamebæ were never destroyed entirely, as is shown by their reappearance in demonstrable numbers, it is quite certain that no such effect is produced by the emetin now as was at first.

The question arises as to whether the patient may not have acquired a certain degree of tolerance for emetin and in some way neutralizes it. That idea is somewhat opposed by the frequent observation that we have made of increased susceptibility to the toxic action of emetin. In one instance of a patient who had been given two courses of daily doses of emetin hypodermically for periods of six days each without any untoward effect, the third course produced a severe enteritis, involving chiefly the colon. Thinking possibly this could have been a coincidence, after the patient had fully recovered, the emetin was given again with even worse effect. After a month it was tried again, and an enteritis which proved alarming started in about thirty-six hours. In another instance a man who had been given a course of one-half grain of emetin hydrochlorid daily for a period of six days without the slightest untoward effect was given another course of six days treatment after an interval of ten days. He developed general muscular soreness and weakness, which almost incapacitated him. After stopping the emetin the trouble gradually improved. The emetin was again given, one-half grain each day, and in three days the muscular soreness and weakness appeared again and became so severe that the patient was unable to walk up his doorstep. It gradually subsided upon the discontinuation of the drug. These instances as well as others indicate that there is a tendency to develop increased susceptibility to certain toxic effects of emetin upon the part of the patient.

Whether strains of emetin-fast endamebæ may not be produced, as is known to be possible with tryponosomes and arsenic, and is supposed to be possible in the case of spirochetes and arsenic or malaria plasmodia and quinine, cannot be stated at this time. In one instance where the endamebæ were not apparently effected by emetin given hypodermically we injected a 1 to 1000 solution of

emetin hydrochlorid into a pyorrhea pocket and also infiltrated the surrounding tissue with the solution. No endamebæ were present twenty-four hours later, but they were demonstrable after an interval of three days. No doubt this was reinfection from the many other pyorrhea pockets in the patient's mouth. This single observation indicates that the endamebæ were still susceptible to the action of the emetin and were not therefore emetin-fast.

No experiments have been made which determine whether emetin introduced into the system does or does not settle or become concentrated in those tissues which also happen to be the site of amebic disease. The instance of apparent special effect upon the muscles of the body and the case of enteritis produced by emetin have been cited. In experimental animals, especially cats, severe and fatal enteritis is produced by continued large doses of emetin.

We have seen two cases and have had reported to us two other cases of severe inflammation of the peridental tissue, undoubtedly produced by emetin administered hypodermically. In one instance there was so much soreness that the patient could not chew food for several days.

Summary. Emetin has specific amebacidal action upon cultural amebæ.

It has similar effect upon the pathogenic endamebæ in amebic dysentery and also those in alveolodental pyorrhea.

There is some important influence, not now understood, which enables the emetin to reach endamebæ in one instance and not another.

There is a certain amount of evidence that Endamebæ buccalis do not become emetin-fast.

DISCUSSION

Dr. C. N. B. Camac: I have listened to the communication of Dr. Bass with much interest. In discussing it I am going to diverge somewhat from the subject of the paper. I believe that in our interest in the endameba, which is as yet an unproved factor in the pathology of oral sepsis, and

especially in general systemic disturbances, we are apt to neglect the pyogenic organisms. Two facts stand out prominently: (1) The mouth and fauces are known foci for serious systemic sepsis. This is no longer a matter of conjecture. (2) No pathological ravages, either local or systemic, have been demonstrated as due to the endameba. I do not wish to minimize Dr. Smith's accurate work, which I had the opportunity recently to have shown me by Dr. Smith in his laboratory. What I do wish to emphasize, however, is that as far as our knowledge goes at present pyogenic organisms are the real mischief-makers, both locally and generally. Future investigation may show a symbiotic action between endameba and pyogenic organisms, or that the endameba are soil-makers for pyogenic infections. It would be a serious error for dentists and internists in the study of this interesting parasite to neglect the pursuit of the terribly destructive and subtle pus-forming organisms. I believe such remarks as timely, because I have found not a few dentists and internists resorting to emetin treatment without making the more troublesome and yet most essential bacteriological studies of the pus-producers, the taking of skiagrams and the employment, in persistent cases, of vaccines. Emetin offers an easy and patient, satisfying treatment. The temptation to employ it is great, but without a painstaking study of the type of infection which is present and the stocking of vaccines the patient is exposed to the grave risk of general infection, in the event of which the physician and dentist would be open to just censure. The endameba as a factor in oral infections and systemic disease has not as yet emerged from the laboratory investigations and till it has been placed firmly among the etiological factors of disease it should not tempt the internists and dentists to temporize with what we now recognize as among the most destructive of the pathological processes.

Dr. L. G. Rowntree: Owing to the many inquiries as to the toxicity of emetin, following the appearance of Dr. Bass' publications and to an accident attending its use in the wards, Dr. Levy and I were led to carry out some toxicity experiments with emetin hydrochloride. Emetin is a powerful poison, and should be considered such. In dogs, daily injections of 1.5 mg. of emetin hydrochloride per kg., repeated for five days almost invariably result in a marked hemorrhagic enteritis and death. Death may ensue after three such doses. Commercial preparations vary much in toxicity and different samples from the same firm show considerable variation.

This is not intended to detract from Dr. Bass' great work. In these days, when emetin is being prescribed so generally throughout the country, often by dentists, it behooves us to remember that emetin is a powerful alkaloid and powerful poison. Its free use is not without danger.

Dr. C. C. Bass: Dr. Rowntree's remarks may be applied with equal propriety to many other drugs in daily use. Emetin is not to be given lightly.

We must have been misunderstood as regards our opinion as to the pathogenecity of Endameba buccalis; we have never presumed to say that it attacks normal tissue or that it produces any systemic effect. We apply emetin in the treatment of Rigg's disease systematically in order to reach all the endamebæ.

THE SIGNIFICANCE OF ACRO-ATAXIA AND PROXIMO-ATAXIA

By C. F. HOOVER, M.D.
CLEVELAND

Acro-ataxia is a term used to designate an impairment in the muscular sense of the intrinsic muscles of the hands and feet in contradistinction from ataxia of the proximal muscles of the upper and lower extremities.

The diagnostic significance of distinguishing between acro-ataxia and proximo-ataxia was first suggested in primary anemia when the differentiation brings out very striking symptoms. Patients with primary anemia complain of paresthesia in fingers and toes and impairment of fine manipulative movements long before there is any impairment in the grosser movements of the extremities. The lower extremities reveal this differentiation far more commonly than do the upper extremities. In the early period of primary anemia a patient will be unable to tell whether the great toe is being passively flexed or extended or twisted; but when the limb is elevated in various positions he will accurately indicate the position of the toe. The former test employs the muscular sense of the intrinsic muscles of the feet. The latter test employs the muscular sense of the iliofemoral muscles.

The anemic patient may lose all muscular sense in the intrinsic muscles of the feet and have no static ataxia, because the muscular sense of the iliofemoral muscles is unaffected. The anemic patient will have the muscular sense of the intrinsic muscles of the hand so impaired that buttoning a waist, washing dishes, sewing, and writing are laboriously and imperfectly accomplished; but when the finger-to-finger and finger-to-nose tests are tried, all indications of ataxia are wanting. In the latter instance we are testing the muscular sense of the thoracoscapular and scapulohumeral muscles

to the exclusion of any function of the intrinsic muscles of the hands. Many patients with primary anemia with pronounced loss of muscular sense of intrinsic muscles of the feet and hands will voluntarily complain only of numbness and tingling, when direct questioning and testing will reveal a loss of the stereognostic sense which in a tabetic patient would render him incompetent for any occupation.

What first attracted my attention to the significance between acro-ataxia and proximo-ataxia was the surprising loss of the stereognostic sense in the hands and loss of all sense of position in the toes in anemic patients when there was not the slightest evidence of any loss of muscular sense in the proximal muscles of the upper or lower extremity, and for this reason the gait was not ataxic, there was no static ataxia, and with the exception of fine manipulations which employed only the hand muscles, there was no impairment of function in the upper extremities. In the later stages of anemia, proximo-ataxia and acro-ataxia are both present.

In spinal-cord disease we see just the reverse. Proximo-ataxia always precedes acro-ataxia. The tabetic patient will have a very pronounced loss of muscular sense in the iliofemoral muscles, with consequent symptoms, long before there is a loss of the sense of position in the toes. He will also lose the muscular sense in his thoracoscapular and scapulohumeral muscles before there is any loss of muscular sense in the hands. Acro-ataxia is seen only in advanced spinal-cord disease.

Primary anemia is a hemolytic disease in which the nervous system suffers, probably from the same toxic substance which acts as hemolysine. This suggests the possibility of employing the differentiation between acro-ataxia and proximo-ataxia as a diagnostic measure to distinguish peripheral nerve lesions from lesions in the spinal cord.

For the past four years all cases of primary anemia with neurological signs and all forms of neuritis, *e. g.*, alcohol, lead, diabetes, and diphtheria, and all syphilitic disease of the spinal cord have been carefully studied with this idea in view. The results have shown that acro-ataxia without proximo-ataxia is seen only in the primary anemias and peripheral neuritis. Proximo-ataxia without

acro-ataxia is seen only in cord disease. In advanced stages of peripheral nerve and cord diseases both proximo-ataxia and acro-ataxia may be present.

This differentiation has served to recognize cases of alcoholic neuritis which have simulated spinal-cord disease. Acro-ataxia may also suggest primary anemia when the patient's color will not suggest anemia. In our cases there were also three diabetic patients with neuritic pains who would have been treated as diabetic neuritis had they not had proximo-ataxia which betrayed the spinal cord as the real seat of the disease. They proved to be cases of syphilis of the central nervous system with glycosuria as a symptom.

One case of carcinoma of the prostate afforded an interesting example of the value of this sign. The patient had mild diabetes for twelve years. An enlarged prostate caused residual urine for two years. During the past year the patient has had much pain in the distribution of both sciatic nerves in the thighs and legs. Proximo-ataxia without acro-ataxia indicated that the neurological signs were not of diabetic origin. The subarachnoid fluid proved to be normal, therefore the cord lesion was due to metastases from a carcinomatous prostate. The prostate was removed surgically and proved to be carcinoma on histological examination. The patient has made a good recovery from his operation, so the character of the spinal-cord lesion still remains in doubt, although at the operation a chain of enlarged lymph glands were palpated along the iliac vessels, a fact which lends additional probability to the carcinomatous character of the spinal-cord disease.

That toxic neuritis may cause proximo-ataxia without acro-ataxia is possible, but we have not had cases which have clearly shown such a combination of symptoms. But during the past four years, during which the relations between acro-ataxia and proximo-ataxia and cord and peripheral nerve disease have been observed, we have failed to find a single case of spinal-cord disease in which acro-ataxia existed unaccompanied by proximo-ataxia. When proximo-ataxia is unaccompanied by acro-ataxia, we have strong evidence that we are not dealing with a disease of the spinal cord.

During the past four years, at Lakeside Hospital we have had

fifty-two cases of primary anemia, and in all of them in which neurological signs were present there was either acro-ataxia alone or accompanied by proximo-ataxia. I have failed to find a single case of primary anemia in which proximo-ataxia existed unaccompanied with acro-ataxia. My experience with all cases seen outside the hospital has been the same.

Another striking experience occurred in primary anemia: Eighteen of the fifty-two cases at Lakeside Hospital were from fifty to sixty-seven years of age, and in sixteen of this number there are records of neurological signs. All these patients, with few exceptions, were seen by myself. In my private practice I have failed to find a single instance of primary anemia of fifty years or older which did not show some neurological signs. In patients under fifty years of age the anemia may be severe and last as long as four years without showing any neurological signs. The first neurological signs to appear in all the primary anemias are the loss of the vibratory sense in the distal portions of the upper or lower extremities and acro-ataxia.

Some of these patients never suffered from anemia. They were not pale, and their hemoglobin during the entire illness never went lower than 75 per cent., and this lasted only a few months. During most of the time there was from 80 per cent. to 95 per cent. hemoglobin (Talquist). The neurological signs, however, progressed just the same as in those patients who were very anemic. They were called primary anemia because they had a venous hum over the bulbus venosus, a high color index, leukopenia, and acro-ataxia and loss of perception of vibrations over the distal portions of the upper or lower extremities. In patients fifty years and older the primary anemia was frequently suggested by the neurological findings. Had it not been for acro-ataxia and impaired perception of vibrations the hematological phase of the disease would have been entirely overlooked.

The fact that the progress of neurological symptoms in primary anemia conforms to those developing in toxic neuritis suggests that the nervous affection in primary anemia begins in the peripheral nerves and ultimately involves the cord. Thus far there have been no histological examinations made which will confirm or deny this interpretation of clinical signs of the disease.

POSTVACCINATION TETANUS: STUDIES ON ITS RELATION TO VACCINE VIRUS

By JOHN F. ANDERSON, M.D.
WASHINGTON, D. C.

Since 1902 the United States Public Health Service has, under authority of an act of Congress, exercised supervision over the manufacture and interstate sale of biological products such as vaccine virus, diphtheria antitoxin, etc. In this supervision the service has considered as coming under its jurisdiction the investigation of certain accidents which, on rare occasions, may follow the use of biologic products, such as the various manifestations of the serum disease or anaphylaxis, severe reactions after the use of bacterial vaccines, and the rare cases of tetanus occurring subsequent to vaccination with vaccinia.

Since 1904 the writer has paid particular attention to cases of tetanus following vaccination and has endeavored to collect accurate data concerning such accidents. These data have consisted, in part, of information in regard to the date of vaccination; result and character; date of onset of symptoms of tetanus; result; whether a shield was used; name of manufacturer of the virus used; samples of the same lot of virus; record of tests made by the manufacturer; number of doses of vaccine of the same lot of virus; and the number of persons vaccinated at the same time. Where it has been possible to secure samples to the same lot of virus used to vaccinate the person later developing tetanus, the virus has been exhaustively examined in the Hygienic Laboratory for the presence of the tetanus organism and its toxin.

A number of the cases have either been investigated by the writer

or by some other representative of the Public Health Service; for data in regard to the remaining cases the information was obtained, as a rule, through the local health officials.

In addition to the data on cases of tetanus following vaccination, there have been collected facts bearing on the number of vaccinations performed in the United States Army and Navy and the prevalence of tetanus among soldiers and sailors during the same period. As will be seen later, the latter data are of especial significance with regard to the theory put forth, by persons opposed to vaccination, who allege that tetanus germs sometimes are present in vaccine virus.

In order that the statistical and clinical data, as well as the laboratory findings, should have an experimental basis, a considerable number of experiments have been made upon animals in the laboratory with reference to the probability of infection with tetanus when animals susceptible to both vaccinia and tetanus were vaccinated with virus known to contain tetanus organisms, *i. e.*, when the germs had been purposely placed therein for experimental reasons. The experimental results will be presented first.

It is known that the rhesus monkey is quite susceptible to vaccinia and also to tetanus. Therefore, to test the possibility of infecting this animal with tetanus through vaccination with virus heavily contaminated with tetanus spores, eight monkeys were vaccinated by multiple vaccinations with such virus.[1] All developed good "takes," which ran the usual course of a successful vaccination. None showed any evidence of infection with tetanus, although the presence of tetanus organisms was shown by examinations made of the crust or scab.

The guinea-pig is acutely susceptible to tetanus and is also susceptible to vaccinia. With this fact in mind, a number of these animals were vaccinated with virus artificially heavily contaminated with the tetanus organism. Many of them developed good "takes," but none showed evidence of infection with tetanus.

It would appear from these animal experiments that, though the virus used for vaccination contained a larger number of tetanus organisms, the bacilli failed to produce tetanus; nor was there

[1] Francis, Edward, Laboratory Studies on Tetanus, Hyg. Lab. Bull. 95, Washington Government Printing Office, 1914.

absorption of sufficient tetanus toxin from the vaccination wound to produce symptoms of tetanus.

During the last thirteen years there has been examined in the hygienic laboratory, specifically for the presence of the organism of tetanus, virus sufficient for the vaccination of over 2,000,000 persons, and in no instance were we able to show the presence of the tetanus germ or its products. The virus examined included samples of the same laboratory number (*i. e.*, the same lot), and in several instances virus from the same package, as that used for the vaccination of persons who subsequently developed tetanus. It is certainly not unreasonable to assume that, had the virus contained tetanus bacilli, the organism would not have escaped detection in the laboratory, especially in view of the thorough mixing of the virus before it is dispensed by the maker.

This is of special significance when we consider that the methods for the detection of tetanus organisms have been so refined in the Hygienic Laboratory that we are able in practically all cases by a combination of tests to show their presence when known to be therein.[1]

It appears, therefore, proper to conclude that the virus so examined did not contain the tetanus organism. And it appears allowable to make the deduction that other portions of the same laboratory number of virus used for the vaccination of persons subsequently developing tetanus also did not contain the germ of tetanus.

An effort was made to ascertain the number of individual doses of vaccine sold by each licensed manufacturer during the ten-year period from 1904 to 1913, inclusive, and it was found that during that time there were sold for use in the United States approximately 40,000,000 individual doses of vaccine virus, and of this number 31,942,000 were not returned to the manufacturers, but were presumably used for vaccination. If the vaccine virus were the source of infection in persons developing tetanus subsequent to vaccination we should expect to find a considerable number of such cases, but I have been able to obtain information of only forty-one authenticated cases. When we consider the small number of cases

[1] Francis, loc cit.

of tetanus and the large number (over 31,000,000) who were vaccinated, we are forced to the conclusion that the infection was not in the virus as sold and used in the United States, but was received in some other way than through the vaccine virus.

In addition, data of a smiliar kind, but with more direct bearing upon cases of tetanus following vaccination, were obtained.

Five cases of tetanus following vaccination were reported within a certain period and an effort was made to find out how many vaccinations were performed in the same State during the period in which these cases occurred. This was done by inquiring as to how many doses of virus were sent into that region, but figures were obtainable from but one distributor, although cases of tetanus had occurred among persons vaccinated with other virus. It was found that 71,796 vaccines had been sold in that State by one maker alone and probably as much or more by others. Moreover, this particular manufacturer had sold during the same period, for use in that State and elsewhere, over 209,000 vaccines; yet no other case of tetanus was reported among the users of that virus.

These five cases were closely studied, and we were fortunate, in several instances, to get the remaining virus, from the package used for the patient or to get the laboratory number, and in this way to examine the laboratory records of the maker in which were set forth the results of the tests of the virus made before shipment. The records showed no evidence of tetanus in the virus examined. The tests of the virus from the same package likewise failed to reveal the presence of tetanus organisms therein. A study of these five cases showed the average incubation period to be twenty-four days, if counted from the date of vaccination.

These various data make it unreasonable to believe that the tetanus in this group of cases was due to the presence of tetanus spores in the virus used, and they support the supposition that the infection with tetanus was received otherwise than through the vaccine virus.

Another line of inquiry was in regard to the number of persons vaccinated in the United States Army and Navy[1] and the number

[1] I am indebted to the office of the Surgeon-General United States Army and the Bureau of Medicine and Surgery, United States Navy, for this information.

of those so vaccinated who developed tetanus. It was believed that such information would be of particular value on account of the large number vaccinated and the completeness of the records. It was found that from 1904 to 1913, inclusive, 359,809 vaccinations were made in the Army and 25,028 in the Navy. In those ten years, six cases of tetanus occurred in the Army, in none of which was there any reason to believe that vaccination had anything to do with the infection. For the same period there were but two cases in the Navy, neither of which bore any relation to vaccination, one case being subsequent to a railroad injury and the other being the result of an infected wound.

It certainly would seem that among this large number of vaccinations, a total of about 585,000, there would have occurred cases of tetanus had the virus prepared and sold in the United States been at fault. This is the more significant, as the virus used in the Army and the Navy is from the same sources as that generally used throughout the country.

The absence of tetanus following vaccination of 585,000 persons in the Army and the Navy is strong evidence in support of the opinion that the reported cases of tetanus following vaccination in the country at large during the period in question were due to infection received in a manner other than through the vaccine virus.

We now come to the reported cases of tetanus which I have investigated since 1904. As few of the cases of tetanus following vaccination were reported in the medical press, use was made of press clippings to trace such cases. Whenever it was claimed that a case of tetanus was in any way connected with vaccination an effort was made to investigate it thoroughly. A total of 41 cases were studied and fairly satisfactory data were obtained covering most of them. A number of additional cases reported as tetanus were found upon investigation not to be tetanus, or were cases of tetanus clearly attributable to infection through injuries or wounds other than vaccination.

In many of the cases studied it was found that other persons had been vaccinated with the same lot of virus at the same time and, with a single exception, no other persons suffered any ill effect. It was also found that many thousands of vaccines of the same lot of

virus were used in other places and no case of tetanus followed their use. In a number of instances samples of the same laboratory number, or even from the same package, as that used for the vaccination of the person developing tetanus were obtained and examined in the Hygienic Laboratory for tetanus; but in no instance were we able to demonstrate the presence of tetanus organisms or toxin in the vaccine virus.

The records of tests of the virus, made by the manufacturers before placing the product on the market, indicated in every instance where it was possible to trace the lot an entire absence of any suggestion of tetanus in the virus, as shown by careful culturing and subcutaneous inoculations in animals. In several instances it was found that shields, usually of celluloid, had been used or that the vaccination wound had been neglected or had been exposed to infection in various ways. The average incubation period, if counted from the time of vaccination to the onset of tetanus, of the 41 cases would be twenty-two days.

Twenty-nine of the cases were fatal and 12 recovered, thus giving a case mortality of 70.7 per cent. for the series. It is interesting to compare these figures with Willson's 52 cases of tetanus following vaccination, in which he found a case mortality of 78.8 per cent.[1] The average incubation period of his 42 cases in which the time was stated, counting from date of vaccination to onset of tetanus, was 19.4 days. The combined figures for the two series are given in the following table:

Series.	Number of cases.	Number died.	Number recovered.	Percentage of mortality.
Willson	52	41	11	78.8
Anderson	41	29	12	70.7
Total	93	70	23	75.2

The average of the supposititious incubation periods, counting from the time of vaccination to the onset of tetanus, in the combined series of 83 cases was 20.7 days.[2]

[1] Willson, Robert N. An Analoses of 52 Cases of Tetanus Following Vaccinia. With Reference to the Source of Infection, 1839–1902. Jour. Am. Med. Assn., 1902, xxxviii, 1147, 1222.

[2] The incubation period in Willson's series was given in only 42 of the 52 cases.

In this connection it is significant to compare the mortality of tetanus due to other causes with regard to the period of incubation and the mortality of the cases following vaccination. It is a well-known observation that the mortality of cases of tetanus with an incubation period of less than ten days is much higher than that of cases with a longer incubation period. In the series of 858 cases of tetanus reported by Anders and Morgan,[1] 588 were found to have an incubation period of ten days or less, and of this number 363 were fatal, or a mortality of 61.7 per cent. There were 270 with an incubation of more than ten days, 112 of which were fatal, showing a mortality of 41.5 per cent.

It will be recalled that the average mortality for the combined series of Willson's and the writer's cases of tetanus following vaccination, 93 in number, was 75.2 per cent. According to the statistics of mortality from tetanus, this corresponds with or is higher than the mortality from cases having an incubation period of 10 days or less. The incubation period of our combined series was 20.7 days, if counted from the date of vaccination.

Now, what is the significance of these figures? We find that in tetanus following vaccination the average period from vaccination to onset of symptoms is 20.7 days, while the average mortality is 75.2 per cent., this high mortality rate being similar to that in cases of tetanus with an incubation period of ten days or less.

It appears evident from this that the infection was received ten days or more after vaccination, and therefore was probably not received through the virus used for vaccination. Many of the cases following vaccination give a history of having the vaccination scab or crust removed in some way, thus permitting infection of the wound, with a reformation of the crust and the establishment of anaërobic conditions. It is to be noted that the scab begins to form about the tenth day or later.

From a consideration of the foregoing the following summary seems permitted:

1. That it is difficult, if not impossible, to produce tetanus in susceptible animals by vaccination with virus containing large

[1] Anders J. M., and Morgan, Arthur C. Tetanus: A Preliminary Report of a Statistical Study, Jour. Am. Med. Assn., 1905, xlv, 314.

numbers of tetanus organisms which have been purposely placed therein.

2. That, in view of the failure to demonstrate tetanus organisms in the large amount of vaccine virus specifically examined for that purpose, it seems exceedingly improbable that vaccine virus as sold in the United States contains tetanus organisms.

3. That from 1904 to 1913, inclusive, over 31,000,000 doses of vaccine virus were used in the United Stases, yet information was obtained of only 41 authenticated cases of tetanus occurring subsequent to vaccination. From this it is concluded that had the vaccine virus used during that time in the United States been at fault many more cases of tetanus should have followed vaccination.

4. That in view of the large number of vaccinations (about 585,000) done in the United States Army and Navy and the absence from them of a single case of tetanus following vaccination, the cases of tetanus following vaccination in the country at large were not due to infection contained in the virus.

5. That the average period from vaccination to onset of symptoms of tetanus in 83 cases of tetanus following vaccination was 20.7 days, while the average mortality of 93 cases was 75.2 per cent., this being slightly higher than the mortality of cases of tetanus due to other causes with an incubation period of ten days or less.

Conclusions. Cases of tetanus occurring fifteen or twenty days subsequent to vaccination do not receive their infection through the vaccine virus, but in all probability the infection is received about the tenth day or later after vaccination.

The infection with tetanus is received by a contamination of the vaccination wound, such as may occur in the infection of any other surgical wound not properly cared for.

DISCUSSION

Dr. George Dock: It is extremely important to have the information contained in Dr. Anderson's communication, but it will not answer the antivaccinationists. They will continue to be fortified by cases originating

from the haphazard way in which vaccination is done and by the prevalent neglect of after-care. Students are taught hip-joints resection and end-to-end anastomosis, but are never told how to perform vaccination. In St. Louis the postvaccination suppurations have been reduced 50 per cent. by the skilled work of the health officers, into whose hands much of this work has fallen. The most shocking suppurations and necroses may be seen in children of practising physicians. Because this operation may be so safe, the common neglect of proper technic should be ventilated.

Dr. John F. Anderson: I think that Dr. Dock has sufficiently emphasized the point that accidents following vaccination in the great majority of cases are due to a failure to recognize that vaccination is a surgical procedure and that the operation and after-care of the wound should be the same as for any other surgical operation.

STUDIES ON THE URIC ACID IN THE BLOOD IN GOUT: SECOND PAPER*

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It is now known that uric acid is constantly present in demonstrable amounts in the blood of man. In 38 patients at the Boston Psychopathic Hospital, Folin and Denis[1] found that the amount of uric acid in the blood determined by their newly discovered colorimetric method varied from 0.7 to 3.7 mgs. of uric acid per 100 grams of blood. Adler and Ragle[2] recently reported the findings in 156 patients examined in the same hospital. The uric acid ranged from 0.7 mgs. to 4.5 mgs. per 100 grams of blood. In 107 out of the 156 cases the amount was between 1 and 2 mgs. In 11 cases there was less than 1 mg. and in 38 cases more than 2 mgs. These cases in both series were unselected. The blood was obtained from newly admitted patients taken seriatim and doubtless included somatic diseases, especially chronic interstitial nephritis, arteriosclerosis, and alcoholism. When classified according to the psychiatric diagnosis, the slight variation in the average amount of uric acid found in each group is striking. The lowest average amount was 1.31 mgs. found in 6 cases of general paresis, the highest, 1.86 mgs. in epileptic insanity, of which disease, however, there was only one case. Adler and Ragle concluded that the blood of insane patients contained the normal amount of uric acid on an ordinary diet. This is probably correct. They are the only figures based on a large number of analyses available for forming even an approximation of the variations in the amount of uric acid that is present in the blood of healthy individuals on an ordinary diet.

* From the Massachusetts General Hospital and the Laboratory of the Boston Psychopathic Hospital.

The view was held until recently that uric acid was not demonstrable in the blood of normal individuals on a purin-free diet. Its constant occurrence with the patient on this diet was regarded as a characteristic feature of gout, and diagnostically important.[3]

McLester,[4] using Folin's method,[5] found uric acid in the blood of fifteen normal individuals who had been on a purin-free diet, for at least three days, in amounts ranging from 0.5 to 2.9 mgs. per 100 grams of blood. A study of his table shows that the average amount was 1.4, while the figures given by Adler and Ragle show that the average amount in their 156 cases was 1.7. That these amounts so nearly agree, deserves to be emphasized, especially as nearly all the individuals studied by McLester were young, healthy adults on a purin-free diet, while the patients studied by Adler and Ragle were of all ages and on a mixed diet.

Very different from these figures are those obtained in gout. In 1913 I reported 11 cases of typical gout in which the uric acid in the blood had been determined by the method of Folin and Denis in Folin's laboratory.[6] At the present time the number of cases studied has been increased to 16. The analyses during the past two years were made by Mr. Ragle and myself in the laboratory of the Psychopathic Hospital. Only those cases are included (1) in which tophi were found; (2) in which a history of characteristic attacks of acute gout was obtained; or (3) in which typical symptoms developed while under observation.

The average amount of uric acid irrespective of the diet or the condition of the patient at the time of the examination was 3.7 mgs. Three of the patients seen during attacks were on an ordinary mixed diet. They had 4.5 mgs., 4.8 mgs., and 5.7 mgs. of uric acid. In the blood of two other patients examined during an attack while on a purin-free diet the uric acid in four determinations ranged from 2.4 to 5.1 mgs., with an average amount of 3.6 mgs. None of these patients was taking atophan.

Seven patients were examined at a time when they were free from symptoms of gout and when they were on a mixed diet. Their blood contained from 3.1 mgs. to 5.5 mgs. The average was 4.3 mgs. In the blood of six patients on a purin-free diet examined at a time when they had no acute manifestations of gout the uric

acid ranged from 1.6 to 7.2 mgs., with an average of 3 mgs. These figures show that in the cases studied there was more uric acid in the blood when on a mixed diet both in the interval and during attacks than when on a purin-free diet. In all, twelve examinations were made when a mixed diet was taken during attacks as well as in the intervals, and the average amount of uric acid was 4.3 mgs. Adler and Ragle, as already stated, obtained an average amount of 1.7 mg. in their 156 unselected psychiatric cases on a mixed diet. A comparison of these two figures shows that there is usually in gout a marked hyperuricemia. In the cases examined there was more than twice as much uric acid on the average than in the blood of non-gouty cases. The same conclusion is reached by taking all the analyses upon which this study is based without regard to the diet, medicines taken, or the condition of the patient at the time of the examination. Thirty-eight determinations were made on sixteen cases of gout, and the average amount of uric acid was 3.7 mgs. per 100 grams of blood.

On a purin-free diet the average amount was larger during an attack than during the interval—in the former 4.3 mgs., in the latter 2.4 mgs. The number of cases is too small to warrant the conclusion that in gout there is usually more uric acid present in the blood during an attack than at other times. That this is the rule, however, is at least suggested by the analysis of all the cases without regard to diet, whether ordinary or purin-free. Eight determinations were made on six patients during an attack, and the average amount of uric acid was 4.6 mgs. Eighteen estimations were made on twelve cases when free from acute symptoms of gout, and 3.3 mg. was the average concentration.

Although these analyses and those of other investigators show that the blood in gout usually contains a relatively large amount of uric acid, the diagnosis of gout cannot be based solely on this finding, as a high concentration is sometimes found in other joint conditions; but in these the hyperuricemia has been transitory, while in gout it is usually constant. In a case of infectious arthritis which did not have the clinical features of gout, the uric acid in the blood at the first examination was 7.6 mgs. The analysis was made by Dr. Denis. Seven months later the blood was again analyzed

and only 0.8 mg. was found, although the patient at the time was on a diet rich in purins. Other similar cases have shown the value of repeated blood examinations.

In typical gout the uric acid may be low at times, even when atophan has not been taken. In one of my patients the first analysis showed only 1.7 mg. of uric acid (purin-free diet), and in the blood of another case on a mixed diet there was 1.9 mg.

In the sixteen cases of gout studied no relation could be traced between the amount of uric acid in the blood and the severity or character of the disease. Two of the patients had many large deposits of sodium urate beneath the skin in different parts of the body. The blood of both contained less than the average amount of uric acid found in gout—one had 2.4 mgs. on a purin-free diet, the other 2.2 mgs. These findings show that the presence of many tophi is no indication that hyperuricemia exists.

The amount of uric acid in the blood bears no apparent relation to the age of the patient.

A considerable variation in the uric acid content may be found in the blood of the same individual within a short time which cannot be attributed to purin in the food. In my first paper I called attention to this fact. A patient admitted in a severe attack of gout had only 2.7 mgs. of uric acid in his blood at the first examination made only twenty-four hours after the purin-free diet was begun. Later the blood contained 5.1 mgs., and he had been fed no food containing purins for fifteen days.

It is not known whether or not the uric acid concentration varies considerably in healthy individuals on a purin-free diet, as sufficient observations on this point are lacking. McLester made four examinations on one healthy person who was on a purin-free diet, and the amount of uric acid was practically constant. But in some cases of gout the variation in the blood at different times may be slight. I examined one case in which the amount of uric acid was unusually low—there was 1.7 mg. present. Nearly two years later a second examination was made and 1.3 mg. found. That two of the lowest amounts of uric acid yet recorded in gout, both well within the limits of normal, with a long interval between the tests, were obtained from the same patient indicates that the

concentration of uric acid in the blood of gout may in some cases be fairly constant.

On the other hand, individuals who have no symptoms or signs of gout may have a wide variation in the uric acid content of the blood. For example, M., a patient with recurrent iritis, had 2.2 mgs. after having been on a purin-free diet for two days. A few months later when on a mixed diet his blood contained only 0.8 mg.

Great fluctuations in the amount of uric acid independent of diet are sometimes observed. This was strikingly shown in a case of primary polyarthritis. (See Table I.)

TABLE I

		Mgs. of uric acid per 100 grams of blood.
McC., aged twenty-two years.		
October.	Ordinary diet	2.7
December.	Purin-free diet	5.0
May.	Purin-free diet	1.6

In another case of chronic non-gouty arthritis the blood at the time of the first analysis contained 7.6 mgs. of uric acid. A few months later when on a diet rich in purins only 0.8 mg. was found.

TABLE II

	Mgs. of uric acid in 100 gms. of blood.		Mgs. of uric acid in 100 gms. of blood.
D. N. Gout. Purin-free diet	3.1	52 hours after eating 280 gms. haddock roe	5.8
		3 days after eating 300 gms. roast beef	6.2
K. Gout. Purin-free diet	2.4	24 hours after eating 270 gms. roast beef	3.0
H. Gout. Purin-free diet	1.7	3 days after eating 150 gms. thymus	3.6
P. Gout. Purin-free diet	2.1	3 days after eating 160 gms. thymus	3.4
J. N. Gout. Purin-free diet	2.2	48 hours after eating 190 gms. thymus	8.7
Average	2.2	Average	5.1

After feeding five gouty patients a meal rich in purins I have observed a marked rise in the uric acid content of the blood above the upper limit of normal. (See Table II.)

In four cases of gout in which the uric acid concentration at the first examination was below the upper limit of normal, 2.5 mgs.,

the blood after this test meal contained a large amount of uric acid.

In the investigation of my first two cases I fed roast beef, but subsequently used sweetbreads for the purin test meal. The patients were placed on a purin-free diet for several days and then a meal of sweetbreads was given. The amount taken ranged from 150 to 300 grams (raw weight). If the patient did not eat the amount ordered at one meal the remainder was given at the following meal. After feeding the sweetbreads the purin-free diet was resumed. The blood was examined after intervals of time ranging in different cases from twenty-four hours to four days. In the three cases of gout tested there was a striking increase in the amount of uric acid in the blood one to three days after the sweetbread meal. In one case after feeding 190 grams of thymus gland the amount of uric acid in the blood was doubled in the first twenty-four hours, rising from 2.2 mgs. to 4.4 mgs. On the third day it reached a maximum of 8.7 mgs. On the fourth day it fell to 2.7 mgs.

This marked disturbance in the uric acid metabolism was not indicated by any apparent delay or diminution in the output of the exogenous purin in the urine; 26.2 per cent. of the ingested purin nitrogen was excreted as uric acid. Burian and Schur[7] found in a normal individual only 25 per cent. of the purin nitrogen of calves' thymus excreted in the urine as uric acid, while a healthy man studied by Pollak put out as uric acid only 15 per cent. of the exogenous purin nitrogen. In the case just cited if the increased output of uric acid comes from the purin bases contained in the sweetbreads then 26.2 per cent. of the ingested purin nitrogen was excreted as uric acid, and this is more than Burian and Schur[7] obtained in a normal individual. It has been demonstrated by Vogt,[9] Reach,[10] Soetbeer,[11] Pollak,[8] Mallory[12], and others that in gout the excretion of exogenous purin is diminished and delayed. That this is not invariably the case was pointed out recently by Magnus Levy,[13] and our study of the blood shows that a marked increase and retention of uric acid in the blood may result from the ingestion of purin bases even when no evidence of retention is found on the examination of the urine.

Before diagnostic importance can be attached to this increase

in the uric acid of the blood produced by the sweetbread meal in gout, the effect of feeding exogenous purins on the uric acid concentration of the blood in non-gouty individuals must be studied. The low amount of uric acid present in the blood of unselected psychiatric patients on a mixed diet (Folin and Denis, Adler and Ragle) shows that a retention of uric acid in the blood in any considerable amount for twenty-four to forty-eight hours rarely occurs; for these patients on an ordinary diet are eating purin-containing food daily, and they might take as much or more purin in their food during the forty-eight hours preceding the blood analysis as is contained in a single sweetbread meal. If the uric acid derived from this accumulated in the blood, the amount found would be considerably greater than that of individuals on a purin-free diet. But the average amount of uric acid found by Adler and Ragle in the blood of patients on an ordinary diet was only 0.3 mg. more than that found by McLester in normal individuals on a purin-free diet.

In four non-gouty individuals the uric acid content of the blood has been determined twenty-four to forty-eight hours after feeding a sweetbread meal. The results are summarized in Table III.

TABLE III

	Mgs. of uric acid in 100 gms. of blood.		Mgs. of uric acid in 100 gms. of blood.
McC. Chronic polyarthritis. Purin-free diet	1.7	24 hours after eating 100 gms. of thymus	2.2
R. Multiple recurrent thrombosis; streptococcus isolated from blood. Purin-free diet	1.8	48 hours after eating 300 gms. of thymus	2.3
M. Chronic polyarthritis. Ordinary diet	2.0	24 hours after eating 225 gms. of thymus	1.8
H. Chronic polyarthritis. Ordinary diet	2.9	47 hours after eating 190 gms. of thymus	2.5
Average	2.1	Average	2.2

On comparing the figures given in the two tables it will be seen that prior to the sweetbread meal the average amount of uric acid present in the blood of the gouty and the non-gouty patients was the same. Twenty-four hours to three days after feeding the

exogenous purin the average amount of uric acid was 5.1 mgs. in the blood of the gouty, while in the blood of those who did not have gout it was only 2.2 mgs.

Exogenous purins in five gouty patients produced a marked hyperuricemia twenty-four hours to three days after they were fed, while in individuals who did not have gout the uric acid concentration was practically unchanged twenty-four to forty-eight hours after the purin meal.

These observations indicated that the uric acid derived from exogenous purin does not accumulate in the blood unless there is a disturbance in the uric acid metabolism. In one patient, however, who had recurrent iritis, but whose history and physical examination revealed no evidence of gout, the uric acid content of the blood was abnormally high two days after a sweetbread meal. His blood on November 1 after having been on a purin-free diet for two days contained 2.2 mgs. of uric acid. On November 7 he ate 150 grams of sweetbreads. Two days later there was 4.8 mgs. of uric acid in the blood. With the sweetbread meal he took two cocktails. It is possible that the alcohol caused a transitory disturbance of the uric acid metabolism. Pollak has shown that a retarded and diminished excretion of exogenous purin may occur in chronic alcoholism. No persistent increase of uric acid existed in my patient as the blood examined on March 30 when on a mixed diet contained only 0.8 mg. of uric acid. This is a lower amount than has been found in any case of gout.

The increase in the uric acid content of the blood in gout after feeding a purin meal may not appear for twenty-four hours or more, and an initial fall has been observed in two cases of gout in which the blood was examined four to eleven hours after the sweetbread meal.

TABLE IV

D. N., aged fifty-eight years. Gout. Chronic interstitial nephritis. Purin-free diet begun March 18.

			Diet.	Mgs. of uric acid per 100 gms. of blood.
March	31.	11.30 A.M.	Purin-free	5.8
		12 noon	300 gms. roast beef	
April	1.	11.30 A.M.	Purin-free	4.6
April	2.	11.30 A.M.	Purin-free	4.5
April	3.	11.30 A.M.	Purin-free	6.2
April	4.	11.30 A.M.	Purin-free	2.8

In Case XV of my series, at 10 A.M., two hours before a sweetbread meal, the blood contained 7.2 mgs. of uric acid. At 4 P.M., four hours after taking the exogenous purin, the uric acid had dropped to 5.8 mgs. and the following morning it was 4.9 mgs. at 11 A.M. It seems remarkable that such a drop in the uric acid content of the blood should occur as a result of taking uric acid forming food into the body. The fall in this case within four hours was 1.4 mg. per 100 grams of blood. This is a considerable amount; in fact, it is equal to the average uric acid content found by McLester in fifteen healthy individuals.

This observation on the blood four hours after a purin meal was made recently, and I have not had the opportunity to repeat it on other cases of gout. In one of the first cases studied, Folin and Denis determined for me the uric acid concentration of the blood eleven hours after feeding a gouty patient, whose diet otherwise was purin-free, 280 grams of haddock roe. Only 2 mgs. of uric acid were found, while at a previous examination 3.1 mgs. were present. Two days after the roe breakfast the amount rose to 5.8 mgs. Although eggs of all kinds and caviar are included by von Noorden[14] in his list of purin-free foods, the output of uric acid in the urine rose 0.13 gram on the day the haddock roe was fed.

In two non-gout cases in which I have examined the blood four to five hours after the sweetbread meal, not only did this drop in the uric acid not occur, but there was a distinct increase in the amount of uric acid.

TABLE V

		Mgs. of uric acid in 100 gms. of blood.
F.	Chronic primary arthritis. Purin-free diet.	
	March 9. 11 A.M.	3.0
	12 noon . 300 gms. sweetbreads	
	5 P.M.	3.7
McC.	Chronic polyarthritis. Purin-free diet.	
	February 23	2.0
	March 2. Four hours after eating 225 gms. of sweetbreads	2.7
	March 3	2.0

The blood of a healthy man three hours after taking an ordinary portion of chicken contained 3.9 mgs. of uric acid. Ten days later only 1.3 mgs. was present.

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OPEN-AIR TREATMENT OF PNEUMONIA AND ANEMIA IN CHILDREN

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The importance of fresh air in the treatment of certain diseases is now well established. The best results from fresh-air treatment are obtained when the air is cold, when it is freely moving in an open space, and when the individual is kept in it twenty-four hours a day.

Little children tolerate poorly the stagnant air of most American houses in winter, and while inappropriate food is perhaps the most important cause of sickness in children, housing in winter is a close second. Severe cases of rachitis develop only in winter and in climates where babies are kept housed, and they develop under these conditions no matter what the food: and children of an ancestry from tropical climates suffer more from the housing than others, notably negroes and Italians.

Between the close, stagnant, indoor air that induces rachitis and pneumonia and the free-flowing, outdoor air there are many gradations due to methods of ventilation. The scientific forced ventilation which is interfered with by the opening of windows is expensive, occupies much space, and is usually inefficient. Open windows give a freshness to the air of a room that is never attained by scientific forced ventilation. The fear of a draught has been deeply impressed on all the last generation and many of the present. Too much access of air for comfort is best avoided by cheese-cloth screens. These were used many years ago by Henry Hun in the Albany Children's Hospital, and are today more satisfactory, I believe, than the patent ventilators made to place under an elevated window sash. In Dr. Hun's Hospital each window had two sets of

sash, one pair carrying glass and the other cheese-cloth. The windows were usually kept open, the air entering freely through the cheese-cloth sash. These wards were always fresh and free from hospital odors, and the children in this institution did wonderfully well. While this method gives one perhaps the best indoor air for those requiring warm, still air, one may obtain far better results in the cold, fresh, outdoor air in winter.

It has long been an accepted fact among certain specialists in diseases of children that exposure to fresh, cold, moving air stimulates the circulation, puts color in the cheeks, increases the vigor of the body, the appetite, and the assimilation of food. While this has been applied particularly to children sick with a limited range of illness, especially pneumonia and tuberculosis, equally good results are derived from the use of this outdoor fresh-air treatment in bronchitis, anemia, chorea, marasmus, and measles as well as in all children lacking in vigor but with no tangible disease.

An excellent explanation of the action of this fresh air on the body functions was made by Howland and Hoobler, who published the results of a series of experiments on children with pneumonia and tuberculosis at Bellevue Hospital, when they reported that they found a marked increase in blood-pressure from putting the children outdoors and an equal diminution in blood-pressure when the children were returned to the closed wards of the hospital. This seemed so rational an explanation that it was generally accepted and hardly seemed to need confirmation, but although several years have elapsed, no confirmation of these results has been published so far as I know.

In work done under the writer's supervision at the New York Foundling Hospital and at the New York Nursery and Child's Hospital by Dr. Schloss no corroboration of these results could be obtained, while at The Roosevelt Hospital, Dr. Hartshorn has carried out a considerable series of blood-pressure experiments, with no constant results. We are thus unable to confirm the results of Howland and Hoobler.

While some children have shown a considerable increase in blood-pressure on being put outdoors, others have shown no increase,

while on the other hand, there has been no constant fall of blood-pressure noted in returning the children to the ward. In fact, we find that the blood-pressure, on the average, is no higher outdoors than in the ward.

Pneumonia of infancy is a disease of housing. It has little tendency to develop in summer and is rarely found in winter in children that are kept in the open air. While for the cure of the disease an agent that is more efficient than any drug or serum or vaccine that is available at present is the freely moving outdoor air, and bronchitis and croup are no contra-indication to the use of this method of cure. A laboratory worker, Dr. A. W. Williams, after reviewing the various methods of treating pneumonia in the *Monthly Bulletin* of the New York City Board of Health, closes her article as follows: "Hygienic treatment, in which absolute rest and free exposure to the outdoor air is the main reliance, seems of late years to have greatly reduced the death-rate, and, until specific therapy is upon a sure footing, will remain the method of choice with most clinicians."

I have been able to carry on some interesting experiments in fresh-air treatment in The Roosevelt Hospital.

The Medical Pediatric Division of The Roosevelt Hospital consists now of a ward of eight beds, a quarantine ward of four beds, and a roof, partly covered by a shed and enclosed on the north, east, and west sides, with seven beds. They all are on the same floor and adjacent to each other, an arrangement that lends itself well to fresh-air treatment.

The bedsteads are painted with white enamel, which is not injured by dampness or wet, and are thus well adapted for this purpose. Ample bedclothes are provided for use in cold weather, as well as sufficient appliances, such as hot-water bags or heaters to keep the extremities warm. Mitts may be needed on the hands, while in very cold weather a cap for the head is desirable. The children are kept on the roof, not for a few hours each fine day, but day and night during all weather. Care is taken, particularly by feeling the feet, to see that the children are comfortably warm; they are brought into the wards only to be changed, bathed, or dressed.

An advantage of such outdoor treatment is the marked lessening of communicability. We have had cases of measles develop on our roof which were followed by no subsequent cases evidently due to these cases. This is an experience rarely met with in hospital wards.

Ten years ago a good deal was written concerning this outdoor treatment of hospital cases, particularly by Dr. Northrup, and while the results obtained continued satisfactory, this method of treatment has gradually fallen into disuse. Moreover, the application of this treatment has usually not been very thorough. A child would be kept outdoors a certain number of hours each day, but rarely have they been kept outdoors all the time.

The conditions which have seemed in our service to be most benefited by this fresh-air treatment are pneumonia, tuberculosis, anemia, chorea, marasmus, and convalescents from any disease. Kidney and heart cases we have thought best to keep in the wards, although one child that had nearly died with endocarditis and pericarditis seemed during convalescence to have been much improved by living on the roof in winter, and this was allowed at his request, and was apparently much enjoyed by him.

I wish particularly to emphasize the fact that our wards are kept cool and well ventilated, so that any comparison between the ward and the roof is a comparison between a fairly open ward and a roof-shed.

The one disease that is most generally accepted as benefited by fresh-air treatment is pneumonia.

The method of treating these cases in The Roosevelt Hospital has been to give them an initial dose of castor oil, put them in beds on the roof, keep their extremities warm and their bowels open. Very few of the cases have received any stimulant or expectorant. In some cases when the cough was troublesome a dilute solution of tincture of chloride of iron in glycerin or water has been used.

Before considering our results of treatment of these pneumonias it will be of advantage to arrive at some idea of the mortality of pneumonia in children. Osler states that the mortality from bronchopnuemonia in children is 50 per cent. Holt gives a mortality of 5 per cent. for lobar pneumonia, but from bronchopneumonia

in private practice from 10 to 20 per cent.; in uncomplicated bronchopneumonia in institution children of 50 per cent. and in complicated pneumonia of from 80 to 100 per cent., while classifying them by age he gives as the mortality of 346 cases during the first year, 66 per cent.; second year, 55 per cent.; third year, 33 per cent.; fourth year, 16 per cent. The mortality of the last 42 cases of lobar pneumonia at the New York Nursery and Child's Hospital, where conditions are very good, was 19 per cent., while that of the last 221 cases of bronchopneumonia was 33 per cent. In the New York Foundling Hospital, where the children are mostly under three years of age, the last 114 cases of lobar pneumonia showed a mortality of 32 per cent., while the last 736 cases of bronchopneumonia gave a mortality of 51 per cent. Of the last 108 cases of pneumonia treated at the Pediatric Service at The Roosevelt Hospital 21 were discharged as improved or unimproved, leaving 87 that remained to the termination of the disease. Of these 87 cases 25 were lobar pneumonia and 62 were bronchopneumonia. Of the 25 cases of lobar pneumonia three died, giving a mortality of 12 per cent., while of the 62 cases of bronchopneumonia 16 died, giving a mortality of 21 per cent.

Many of these cases were complicated: one turned out at autopsy to be tuberculosis, and in others death really was precipitated by other diseases. Perhaps the best estimate of our results is obtained by considering our uncomplicated cases of pneumonia: The 21 cases of uncomplicated lobar pneumonia showed one death in a child of six months, giving a mortality of 4.7 per cent., while the 31 cases of uncomplicated bronchopneumonia showed only one death in a child of nine months, giving a mortality of 3.3 per cent.

These uncomplicated cases of bronchopneumonia ran an average course after admission of seven days, and the cases of uncomplicated lobar pneumonia ran an average course after admission of three days.

One case of particular interest was that of a colored boy, aged five years, who came into the hospital with typhoid fever. He ran the ordinary four weeks' fever, followed by a relapse of two weeks, at the end of which time, after having been in the ward eight weeks, he developed pneumonia and was immediately put on the roof.

The pneumonia involved first the right upper lobe, then the left lower and the right middle lobe. The breathing was bronchial on the right side, and soon we found developing on our Röntgen-ray plates two cavities in the right middle lobe. These became larger, the sputum became foul, and physical signs of these cavites developed. The boy was desperately sick for a long time, but was finally discharged eighteen weeks after admission, with a practically normal temperature. He has since made a good recovery and has been at school during the past winter. This boy would, I believe, have certainly died if he had not been put on the roof.

Recently he has been returned to our ward with signs of consolidation over the right middle lobe, with a Roentgen-ray plate that shows the presence of the old cavities with consolidation in the neighborhood, and areas that are fairly typical of tuberculosis. He was running a moderate temperature, with marked remissions, and was vomiting on admission. During the days he has been on the roof his temperature has become more moderate, he has stopped vomiting, his appetite has improved, and his last roentgenogram shows a marked clearing of the areas of consolidation in his lungs.

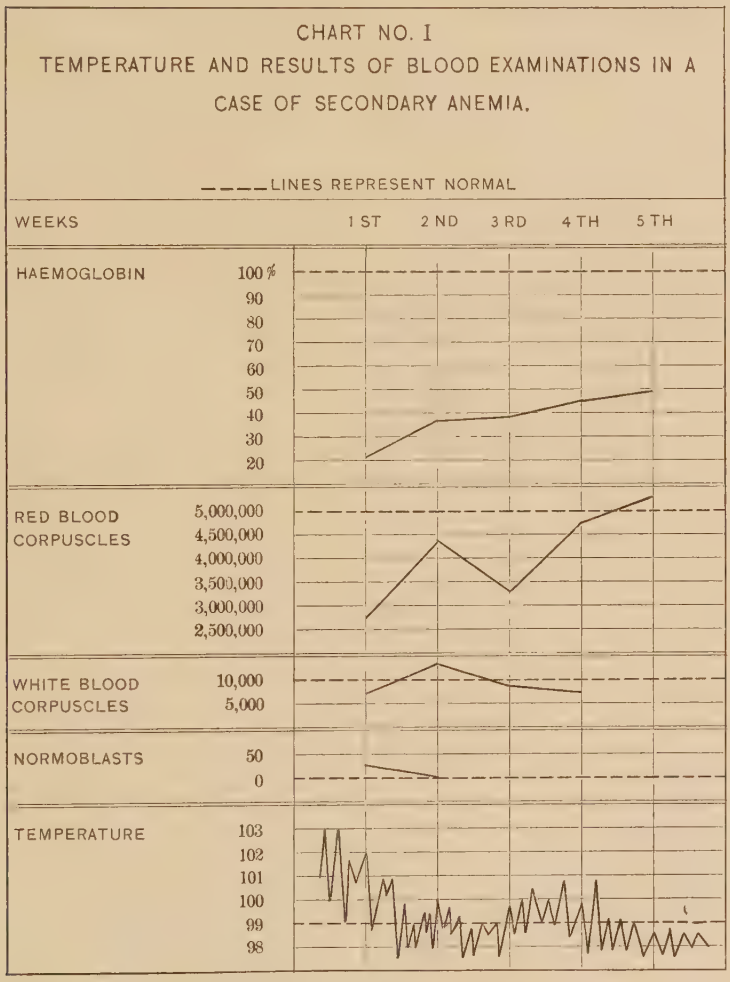
Perhaps our most interesting results of the roof treatment have been in the cases of abnormal conditions of the blood. One simple anemia made a wonderfully speedy recovery, with little medicine and roof treatment.

A poorly nourished child, aged thirteen months, came to our service running a considerable temperature of from 101° to 103°, with bronchitis, gastro-enteritis, and a marked simple anemia. The hemoglobin was only 22 per cent.; red cells, 2,840,000; white cells, 7700. There was moderate poikilocytosis and anisocytosis (Chart I).

This child was given seven drops of syrup of iodide of iron three times daily in addition to the treatment on the roof. The improvement was very rapid, the temperature in a week having reached normal, while in four weeks from admission the hemoglobin was 45 per cent., and the red cells 5,030,000. The weight had increased one pound. The respirations had fallen from 38 to 29. The pulse had dropped from 136 to 100. The rapid improvement of this child is well shown on Chart I.

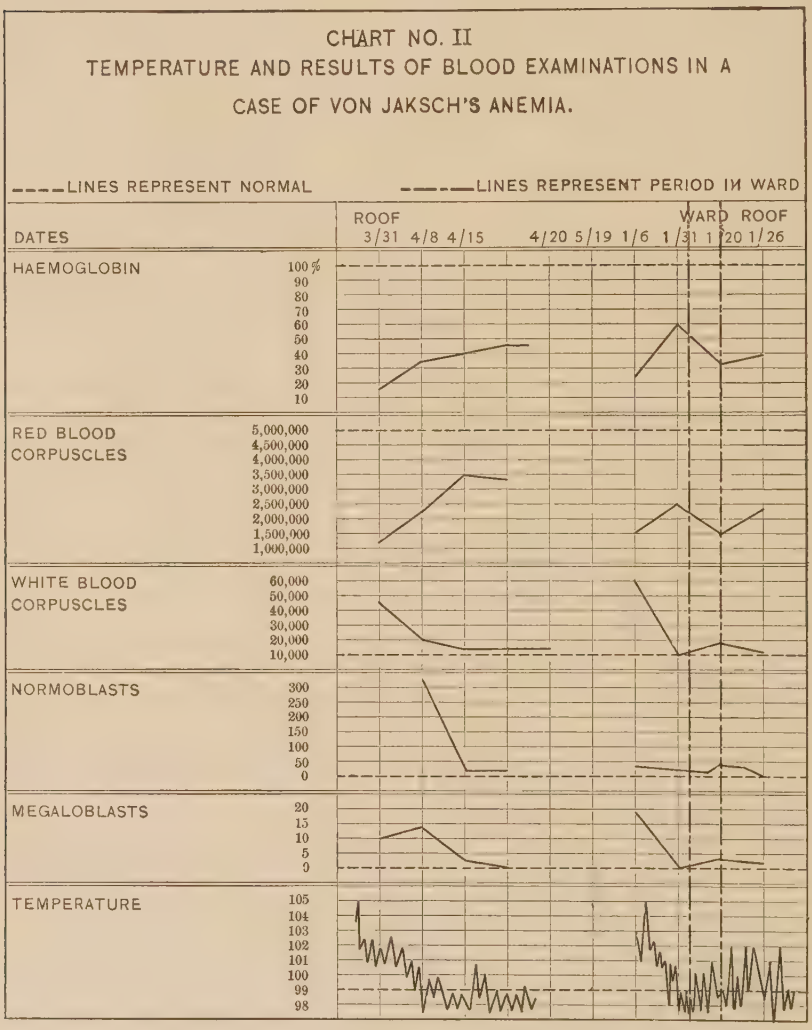
A very marked case of von Jaksch's anemia occurred in a colored child, a Porto Rican, aged three years. The child complained of fever and headache, had a large spleen, and ran a temperature

CHART NO. I
TEMPERATURE AND RESULTS OF BLOOD EXAMINATIONS IN A CASE OF SECONDARY ANEMIA.



of 102° for ten days after admission. She was put on the roof and was given no medicine excepting such as might have been necessary to keep her bowels open. Her blood count on admission was: Hemoblogin, 17.5 per cent.; red blood cells, 1,368,000; index,

0.77; white blood cells, 41,000; polynuclears, 74 per cent.; lymphocytes, 26 per cent.; megaloblasts, 10; anisocytosis and poikilocytosis. The blood count showed a markedly typical von Jaksch's anemia condition.



Eight days later the blood had improved, as shown on Chart II. The next week showed still further improvement, the normoblasts and megaloblasts having nearly disappeared, while on April 29

the child was so well that she was discharged, the spleen, however, remaining large.

Six weeks later the child returned with pneumonia, the blood, however, being much the same as when the child was discharged, showing none of the changes characteristic of von Jaksch's anemia. The child made a recovery on the roof from pneumonia and was not seen again until last January, when she came in with the following blood count: Hemoglobin, 25 per cent.; red blood cells, 1,600,000; index, 1.1; white blood cells, 50,000; polynuclears, 70 per cent.; lymphocytes, 27 per cent.; myelocytes, 3 per cent.; normoblasts, 48; megaloblasts, 18. Anisocytosis and poikilocytosis. Red blood cells: largest, 12.6 m.; smallest, 2.1 m.

The spleen remained about the same size. Normoblasts and megaloblasts were present in considerable numbers, and there was a considerable increase in the number of white cells and a diminution in the red cells.

One week on the roof almost eliminated the normoblasts and megaloblasts and brought the white cells down to normal. At that time it occurred to me that the improvement in the child's condition might not be due to the roof treatment but might be due simply to hospital care. Therefore on January 20 the child was put in the ward. The temperature immediately began to rise, and although we had contemplated leaving the baby in the ward for a week, on the sixth day the child was doing so badly it was felt that it was not fair to leave her there any longer, and she was taken to the balcony. At that time the blood had changed as follows: Hemoglobin, 33 per cent.; red blood cells, 1,600,000; index, 1.2; white blood cells, 17,400; polynuclears, 60 per cent.; lymphocytes, 32 per cent.; myelocytes, 8 per cent.; megaloblasts, 4.

After a week on the balcony there was a marked improvement in the blood count, as indicated below: Hemoglobin, 36 per cent.; red blood cells, 2,400,000; index, 0.9; white blood cells, 14,400; polynuclears, 56 per cent.; lymphocytes, 35 per cent.; myelocytes, 0; normoblasts, 2; megaloblasts, 1.

During this time the child's temperature returned to normal, but, unfortunately, she showed gonococci in a vaginal smear and had to be transferred.

Chart II shows well the approach to normal of the abnormal condition of the blood as well as the lowering of the temperature while on the roof; the return toward the original condition on admission during the six days in the ward, and the subsequent improvement on the roof.

A third child, aged four years, of French and German parentage, a case of leukemia, gave a history of cough for four months, swelling of the neck for four weeks, dyspnea, constipation, pains in legs and arms, anorexia, and fever for a few days. He had dysentery when six months old. His complexion had always been yellow.

Physical examination showed a fairly well-developed boy, with skin so dark as to suggest mulatto blood. He was evidently anemic and looked sick. There was slight dyspnea, with inspiratory stridor and slight cough. The tongue was moist and clear. The teeth were decayed. There was a general enlargement of the lymph glands all over the body. The parotid and submaxillary glands were markedly enlarged but not tender, while large masses of lymph nodes filled up the neck. Large groups of lymph nodes were in both axillæ, extending out over the anterior chest wall. The epitrochlears were felt, and the inguinal glands were markedly enlarged. The chest showed a diminished excursion on the left side. There was on the same side some dulness, with, however, a rather tympanitic note over the scapula. There were a few moist rales on this side, with diminished breathing of a somewhat bronchial type. The abdomen was large, showing a markedly enlarged liver and spleen, as indicated in the sketch (Fig. 1), the spleen extending seven and one-half inches below the free border of the ribs in the mammary line and one and one-quarter inches to the right of the midline at the navel.

The blood count showed: hemoglobin, 30 per cent.; red blood cells, 2,000,000; white blood cells, 158,400; neutrophiles, 2 per cent.; basophiles, 1 per cent.; small lymphocytes, 5 per cent.; large lymphocytes, 90 per cent.; turik irritation, 2 per cent.; anisocytosis and poikilocytosis.

The Roentgen-ray plate showed a consolidation of practically all of the left lung, while an exploratory puncture of the left chest withdrew a few drops of turbid amber fluid.

This child was placed on the roof where, as may be seen by Chart III, the white cells dropped in twenty-four hours from 158,400 to 15,000. The general appearance improved and the child began to get color in his cheeks. Each Roengten-ray plate showed further clearing up of the pneumonia and physical examination showed a diminution in the size of the spleen, so that on the thirteenth day

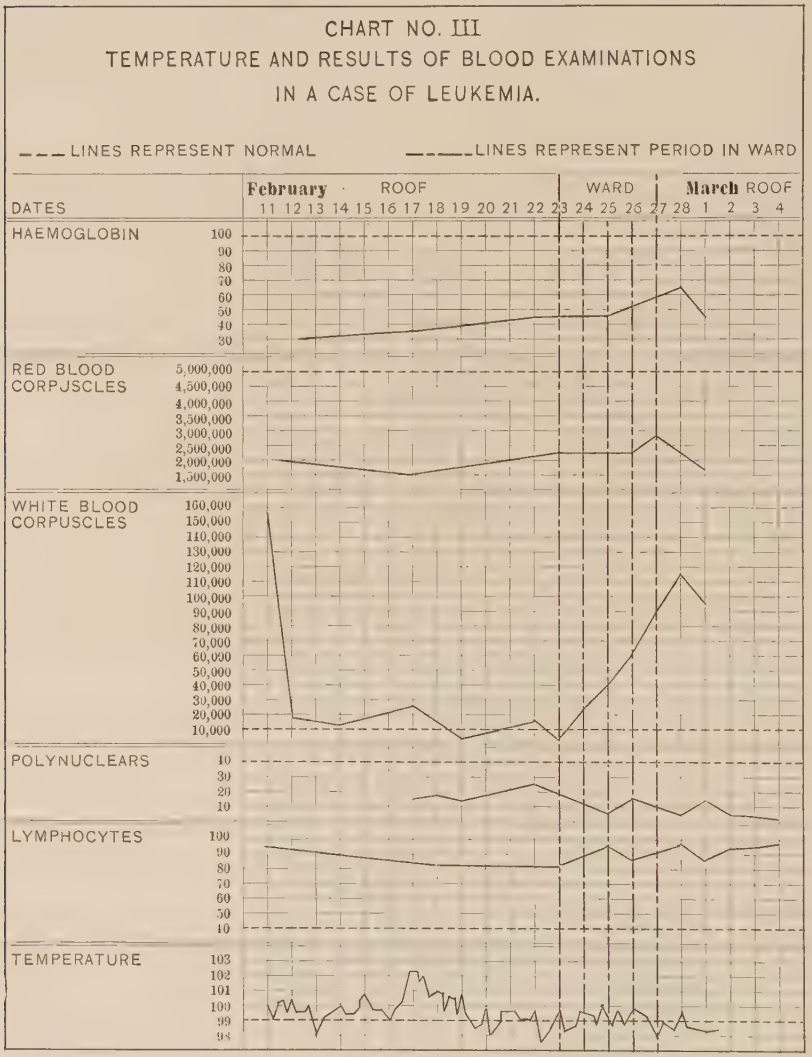
Fig. 1.—The child with leukemia, showing lymph-node enlargement indicating the lower border of the liver as well as the outline of the spleen.

after admission all the lymph nodes as well as the salivary glands having diminished in size, the spleen having contracted from seven and one-half to four and one-half inches below the free border of the ribs and no longer coming forward to the median line, a considerable portion of pneumonia having cleared up, as shown by the Roentgen-rays, and the blood having a normal number of leukocytes and being improved in other respects, the child was put in the ward. In this

ward during a considerable part of the time that the child was in it, the windows at both ends were open and it was always well ventilated.

CHART NO. III

TEMPERATURE AND RESULTS OF BLOOD EXAMINATIONS IN A CASE OF LEUKEMIA.



At the end of four days in the ward the lymph nodes were as large as they were on admission. The spleen had again extended beyond the median line, and to seven and one-half inches below

the free border of the ribs. The leukocytes, which had been daily increasing, had reached again 90,000, so that it seemed unfair to keep the child longer under these conditions, and he was again removed

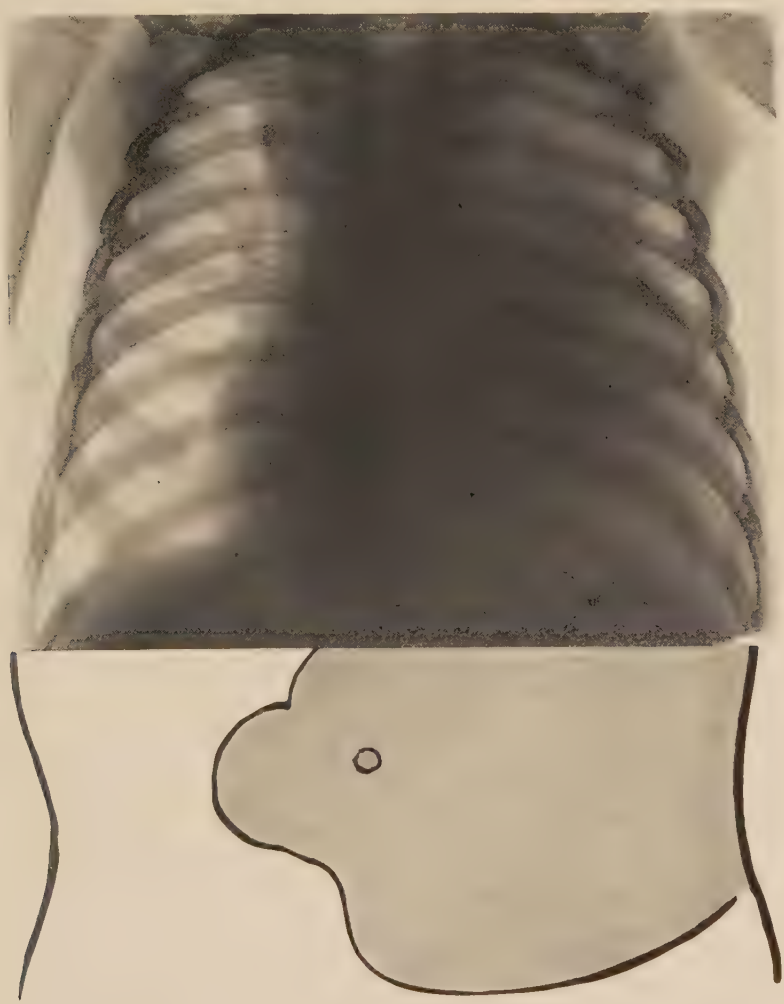


FIG. 2.—Leukemia case on admission, showing size of spleen and shadow in left lung.

to the roof. Fig. 3 shows well the diminution in the shadow made by the left lung and the diminution in size of the spleen after the patient had been on the roof twelve days, while Fig. 4 shows the disastrous effect of only four days in a well-ventilated ward.

It is, of course, evident that three cases of sickness associated with abnormal conditions of the blood are not sufficient for drawing any conclusions, but in at least two of these cases it does seem as

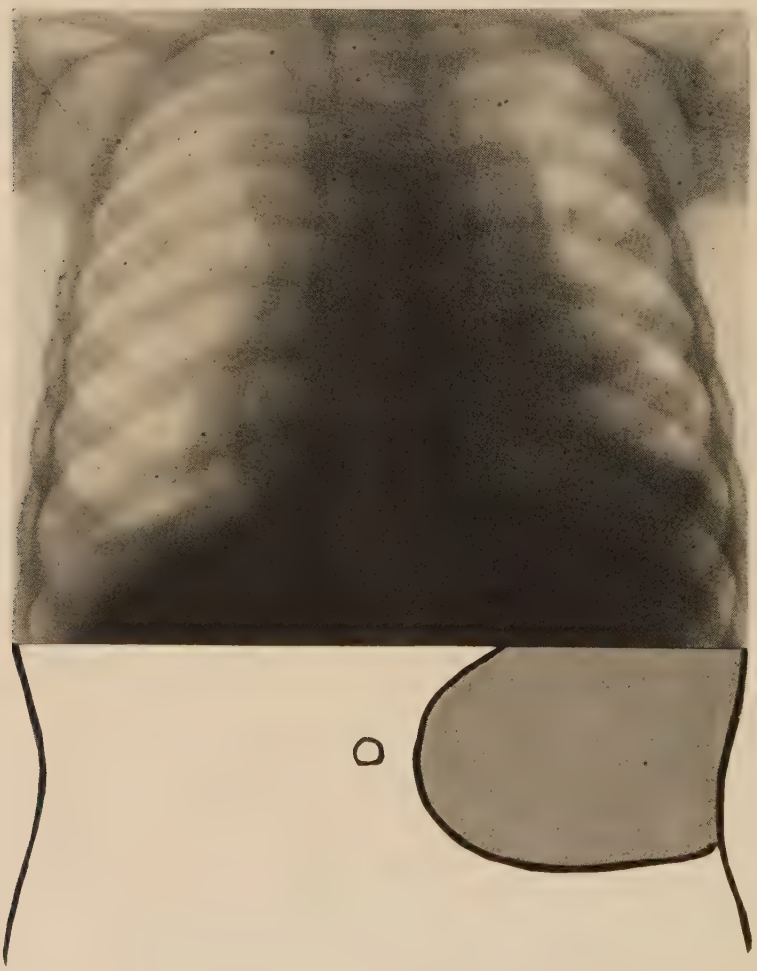


FIG. 3.—Leukemia case after twelve days on the roof, showing diminution in shadow made by left lung and diminution in size of spleen.

if a fairly reliable demonstration of the influence of fresh air alone had been made.

Summary. Treatment of children in an open-air shed in winter increases their vitality and resistance to disease more powerfully than medicines.

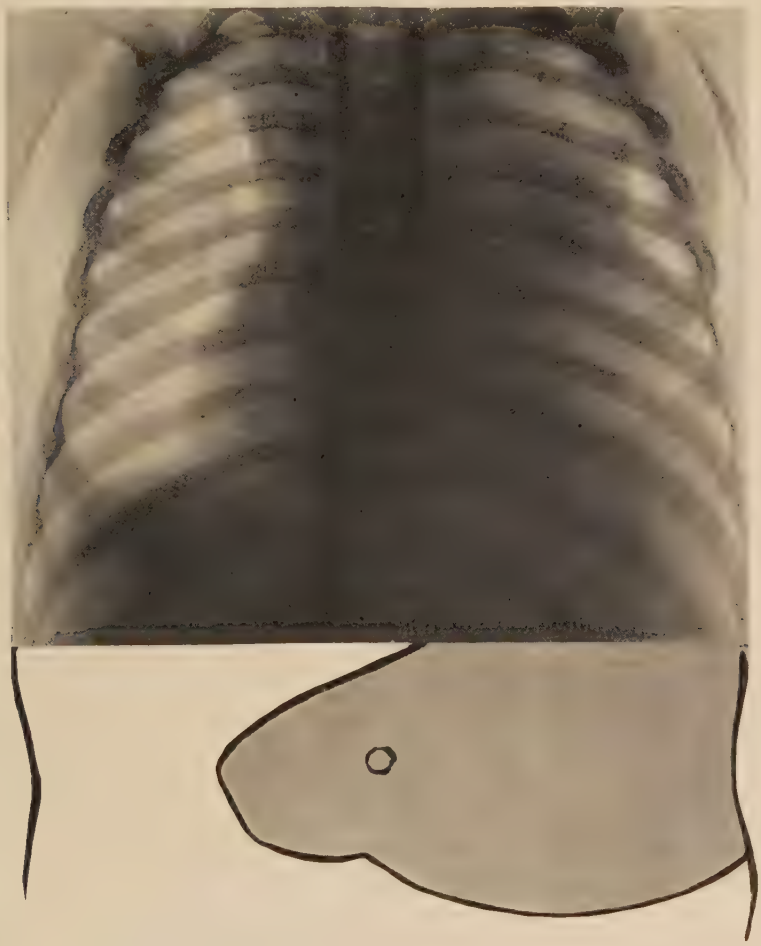


Fig. 4.—Disastrous effect on leukemia case of only four days in a well-ventilated ward.

Pneumonias run a short course and show a very low mortality Certain abnormal conditions of the blood will rapidly improve with little or no medical treatment.

THE ISOLATION IN CRYSTALLINE FORM OF THE COMPOUND CONTAINING IODIN WHICH OCCURS IN THE THYROID; ITS CHEMICAL NATURE AND PHYSIOLOGICAL ACTIVITY*

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Previous investigation has shown that the thyroid exerts marked physiological activity when administered to the normal animal and man, and that the removal of the gland is followed by profound changes. The extremes of thyroid disturbance are seen in the two syndromes, exophthalmic goitre and myxedema. Between these extremes are many indefinite or borderline conditions so that thyroid disturbances present a confusing mass of evidence which is not easily diagnosed or classified. Clinically, the cases have been classified and a basis of diagnosis established. Much light has been thrown on the progress of the disease of exophthalmic goitre, and the physiological properties of the toxic substance responsible for the symptoms have been described.[1]

From clinical observations the thyroid has been supposed to have a secretion which contains a substance or substances capable of producing certain physiological activity. But the acceptance of such a theory in itself erects a barrier beyond which the clinician cannot go. The only passage of that barrier is a method which will unlock the consituents of the thyroid secretion and separate the active substances in pure form. Definite conclusions could not be arrived at as long as these substances were known only by the symptoms produced by their presence or absence.†[2]

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† No comprehensive review of the clinical and pathological aspects of thyroid disturbance is attempted in this paper. For discussion of these and a presentation of the views held in our clinic reference is made to Wilson's article under reference 2.

What is the substance in the thyroid that produces toxic symptoms? What is the relation of iodin to thyroid activity? Is the iodin in the gland present in a hitherto unknown substance specific for the thyroid? What is the compound in the thyroid essential for normal life? Does the thyroid secretion contain more than one active constituent? Can the active substance or substances be separated from the gland in pure form and retain their activity? These and many more problems can be answered only by separation in pure forms of the substances in question, and by investigation of their physiologic activity.

Attempts to isolate the active principle have resulted in preparations which may be divided into two classes: (1) those secured by separation of products of protein nature without decomposition or destruction of the protein molecule, and (2) those obtained by means of hydrolysis of the protein and the subsequent separation of the decomposition products. In the first class of preparations are Oswald's[3] thyroglobulin and iodin-free nucleoprotein. Other investigators have prepared similar proteins from the thyroid. These products, which are original protein compounds unchanged in chemical nature, still retain their activity, as shown in the treatment of symptoms of cretinism and myxedema. In the second class of preparations, Baumann's[4] iodothyrin, containing about 9 per cent. of iodin, is the result of decomposition of the proteins with sulphuric acid. The iodothyrin so obtained is about 4 per cent. of the total weight of the dried thyroid. Other decomposition products have been obtained by Hutchinson[5] working with pepsin and trypsin on the thyroid proteins. Hutchinson separated in this way a product containing 3.6 per cent. of iodin.

Another means of throwing light on the nature of the iodin compound has been to prepare various iodin compounds and test the physiological activity of these. Di-iodotyrosin, tetra-iodohistidin, tri-iodo imidazol, iodized tryptophan, and iodized phenylalanin and other organic compounds have been tested in this way, but no compound has been found which produces effects similar to those of desiccated thyroid.

This paper contains a summary of an investigation of the chemical constituents of the thyroid. The object of the work was to isolate

in pure form one or more chemical compounds which possess physiological activity. Dialysis was used as a preliminary study of the proteins of the gland and the nature of iodin combination. Desiccated thyroid, either in suspension or dissolved in dilute alkali, was found to lose less than 5 per cent. of its total iodin by dialysis in a collodion sac against running water. Experiments were then made varying the temperature and acidity of the dialysate. These results showed that increase in temperature and acidity favored dialysis of the iodin compound, and as much as 40 per cent. could be made to pass through the sac in this way. Attempts were then made to alter the nature of the proteins to see the attending influence on dialysis of the iodin. Boiling in strong sodium hydroxide allowed 80 per cent. of the iodin to pass the dialyzing sac. Boiling with sodium hydroxide and hydrogen peroxide allowed 94 per cent. to pass.

These results showed a decomposition of the protein and a probable splitting off of iodin in the inorganic form. As such vigorous treatment would undoubtedly destroy physiological activity, further experiments were conducted to find some treatment which would break down the complex proteins into simpler products without destruction of the compounds so obtained. Alcohol was tried as a medium for the carrying out of such treatment. Alcohol saturated with hydrochloric acid gas was tried as a hydrolytic agent, but no satisfactory cleavage resulted from its use. Hydrolysis with sodium hydroxide in alcohol was then tried, and it was found that this method produced a cleavage different from any of the others. Seventy-five per cent. of the iodin was dialyzable, but it was easily shown that the iodin was not split off as sodium iodide, but still existed in organic combination. After it was shown that sodium hydroxide in alcohol altered the nature of the protein to a marked degree, dialysis, as a criterion of the nature of the iodin combination, was discontinued, and a detailed study of the chemical properties of these products of hydrolysis was begun.

No specific precipitant was found for the iodin compound in either an alcoholic or aqueous solution. After many attempts to find such a reagent it became apparent that the iodin was present in two different forms of organic combination. About 50 per cent.

of the total iodin was soluble in acid and 50 per cent. was insoluble. As the solubility in acids affected a separation between the two apparently different iodin compounds, this treatment was used as the first step in the separation of the products of hydrolysis. Those compounds insoluble in acid are designated constituents of Group A, and those soluble, constituents of Group B.

All the constituents of Group B are easily dialyzable. Saturation of a solution of B with ammonium sulphate produces a sticky, tarry precipitate which evidently consists of amino-acid complexes and carries down with it about 80 per cent. of the iodin in B, showing that it is still present in organic combination.

The iodin compound in B is precipitated to a large extent with mercury sulphate, and almost quantitatively with silver sulphate in the presence of magnesium oxide. A large percentage of the iodin is split off by this treatment. Oxidizing agents, even copper acetate, also easily split off the iodin from its organic combination.

After establishing the general chemical properties of Group B, efforts were directed to a more extended study of Group A. The most striking chemical property of A is its acidic nature. All the constitutents of A are easily soluble in dilute alkali or ammonia, and are reprecipated by any acid stronger than carbonic acid.

Experiments with organic solvents showed that uncombined sulphur, fatty acids, and about 10 per cent. of the iodin in A is soluble in ether. The fatty acids doubtless came from the fats which were saponified by the alkaline alcohol and the sulphur probably resulted from the decomposition of cystine. Further experiments showed that the solubility of the iodin in organic solvents varies greatly, it being least soluble in petroleum ether. The second step, therefore, for the purification of A is the removal of fatty acids and sulphur by extraction with petroleum ether. The product thus obtained contains about 4 per cent. of iodin, and this preparation may be dissolved in alkali and reprecipitated with acids without appreciable loss of its total iodin. This treatment slowly removes some constitutents containing nitrogen but no iodin, so that the percentage of iodin in A may thus be increased to about 6 per cent.

This preparation is a dark brown powder insoluble in water and

acids, easily soluble in dilute alkali and ammonia. Its alkaline solution is precipitated by copper hydroxide and to a large extent by barium, calcium, and magnesium salts. It is almost entirely soluble in ethyl acetate, but by partial extraction with this solvent it is possible to separate A into two fractions. In the ethyl acetate soluble portion of A the percentage of iodin is increased to 13 or 14 per cent., but the ethyl acetate insoluble fraction contains only 1.5 per cent. iodin.

Except for the solubility in ether the general chemical properties of A closely resemble those of a fatty acid. By further hydrolysis of the A group the compound containing iodin has been separated

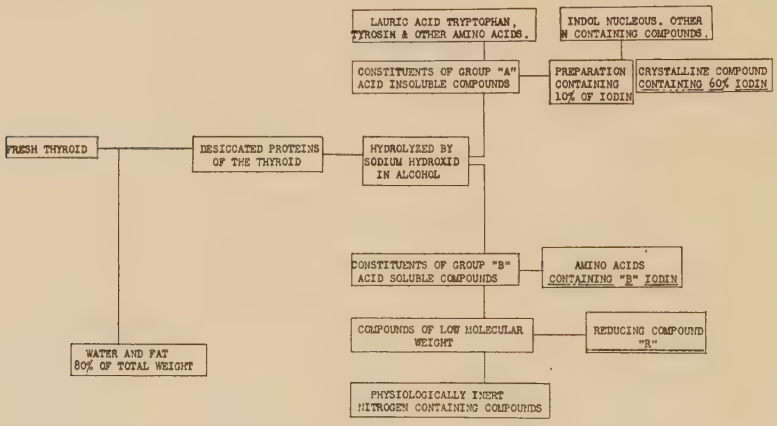
LAURIC ACID TRYPTOPHAN, TYROSIN & OTHER AMINO ACIDS.
INDOL NUCLEOUS. OTHER N CONTAINING COMPOUNDS.
CONSTITUENTS OF GROUP "A" ACID INSOLUBLE COMPOUNDS
PREPARATION CONTAINING 10% OF IODIN
CRYSTALLINE COMPOUND CONTAINING 60% IODIN
FRESH THYROID
DESICCATED PROTEINS OF THE THYROID
HYDROLYZED BY SODIUM HYDROXID IN ALCOHOL
CONSTITUENTS OF GROUP "B" ACID SOLUBLE COMPOUNDS
AMINO ACIDS CONTAINING "B" IODIN
COMPOUNDS OF LOW MOLECULAR WEIGHT
REDUCING COMPOUND "R"
WATER AND FAT 80% OF TOTAL WEIGHT
PHYSIOLOGICALLY INERT NITROGEN CONTAINING COMPOUNDS

CHART I.—Chemical constituents of the thyroid.

in pure crystalline form. Its exact formula cannot now be stated but it appears to be di-iododi-hydroxy-indol. It crystallizes in microscopic needles that melt around 220° C. It is very insoluble in alcohol, ether, water, acids, and sodium carbonate. Dilute hydrochloric acid dissolved 1 part in about 200,000. It is readily soluble in dilute alkali and ammonia. (Chart I).

The thyroid having been separated into several different constitutents, it seemed desirable to test each one for its possible physiological activity. These preparations were first tested with normal dogs kept in metabolism cages. Administration of Group B constituents by mouth or by subcutaneous or intravenous injection

produced no apparent effect on the temperature, blood-pressure, pulse rate, nitrogen balance, or weight. Administration of Group A constituents by mouth or subcutaneous injection produced the typical so-called hyperthyroid symptoms: increase in pulse rate slight increase in temperature, marked increase in nitrogen elimination with loss of weight, increase in nervous irritability, and tremor.

These results showed that the toxic symptoms following administration of the gland can be produced by a small group of constituents which amount to only 4 to 5 per cent. by weight of the desiccated thyroid.

Further investigations concerning the injection of Group A constituents were carried out on a large number of dogs under varying conditions. A typical result is as follows: Weight of dog 10 kilos; pulse rate during previous ten days, 90; 200 mgs. of A used for each injection. Following the injection there is no immediate effect on the temperature, pulse rate, or blood-pressure, and twenty-four hours after the injection there is still no apparent change. The substance injected seems to be inert, but at this time another injection of 200 mgs. is given and the observations continued. From thirty-six to forty-eight hours after the first injection the dog appears restless, the temperature is slightly increased, and the pulse rate has reached 120. The observations and daily injections are continued. On the fourth or fifth day the dog is in a highly nervous condition, restless, with tremor, and there is generally severe diarrhea; the pulse rate is between 200 and 250. Beside the high rate, the pulse has changed its character, becoming hard and hammer-like, with spasms of tachycardia. Although the daily injections are continued at this time, the dog rapidly becomes better, the pulse rate decreases to about 120, and the hard, pounding effect disappears. If the injections are now stopped the dog returns to normal, the pulse rate even dropping to 68 to 70 in some cases.

Nature of the Toxic Compound. Having shown that toxic effects are produced by a certain group of constituents of the thyroid, attempts were made to determine the chemical nature and to isolate in pure form the toxic substance contained in this group of compounds.

The presence of iodin as a normal constituent of the thyroid has

been known for nineteen years.[4] During this time many controversies have arisen out of attempts to explain the relation between the physiological activity and the presence of iodin.[7 8 9 10 11 12 13] From the beginning of this investigation the isolation of the compound containing iodin was held as the main objective, hence the iodin content of the various preparations of the A constituents was always determined.

By the use of A made from beef, hog, sheep, and pathological human thyroid it was readily shown that the toxicity of A is directly proportional to its iodin content. By extracting A, containing about 5 per cent. of iodin with ethyl acetate, it may be fractioned into two parts: one containing about 9 per cent. of iodin and the other 1.5 per cent.; but, taking iodin as the standard and the effect on the pulse rate as the criterion, both these preparations produced toxic effects. This indicated that the active substance in each case was the compound containing iodin, and that this substance was combined differently in the two preparations.

The toxic effects of A were first produced by preparations containing from 4 to 5 per cent. of iodin. Later the A constituents were further broken down and a purer form, containing 25 per cent. iodin, was obtained. Injection of this under the same conditions, using iodin as the standard, produced the typical effects.

Finally, the iodin-containing compound was isolated in pure crystalline form having a constant iodin content of 60 per cent. These pure white crystals used in amount equivalent to previous injections, keeping A iodin as the standard, produced the typical symptoms with the same severity. We can, therefore, conclude that the substance in the thyroid responsible for the production of toxic symptoms is the compound containing A iodin, and that this compound can be separated in pure crystalline form without loss of its activity (Fig. 1).

To determine whether the sudden improvement in the general condition following a series of injections of A resulted from the development of a tolerance to the A compound, a dog was injected until in a highly toxic condition, and was then allowed to return to normal. To a second dog two series of injections were given, the second series being precisely similar to the first. Under the effect

of the second series the dog lost weight, had severe diarrhea, became nervous, and appeared to react as severely as during the first series except in regard to the pulse rate. At no time was the rate as high, and it did not develop the hard, pounding property to such a degree. The other symptoms followed much the same course as during the first series. To a third dog three series of injections were given, the previous conditions being observed. Again, the dog reacted as before, but after the third series appeared less capable of throwing off the toxic effects. While the pulse rate was not high, there were spasms of tachycardia when the rate reached 280 to 300; but when quiet and not under excitement the rate was about 150.

These and other results indicate that the A iodin compound does not work in a rapid and direct manner, and that some form of tolerance is produced. Further experiments are being carried out to explain more fully the factors involved.

Therapeutic Effects of A and B in Man. The physiological results on dogs established the general toxicity of A and the non-toxic effect of B sufficiently to warrant the use of these preparations for therapeutic purposes in cases of thyroid disturbance, and during the past three years many patients have been treated.

As repeated injections over long periods are impracticable in man, the split products were always given by mouth. The results obtained may be briefly stated to be entirely in accord with the preliminary tests on dogs. No toxic effects have ever been produced by the B constituents, although more than 200 patients have been treated; but the A constituents, even in small amounts, produce toxic effects.

The severity of the toxic effects following administration of A to normal individuals varies greatly, but in general it is as follows: If to a normal individual with a pulse rate of about 75 and a weight of about 75 kilos sufficient A is given per day to contain 3 mgs. of A iodin, on the day following the first dose there is no apparent change except a slightly increased pulse rate. If the same daily dose is continued the patient slowly reacts, and in the course of eight or ten days nervous symptoms develop, the pulse rate is around 130 to 140, there is a tendency to perspire more freely on

exertion, and the patient may be short of breath and easily tired. At first there is an increased appetite, but later loss of appetite, nausea, and sometimes diarrhea develops. During this time the patient usually loses weight, from 1 to 5 kilos (idiosyncrasy ?). If smaller doses are given the severity and course of symptoms are modified, but the patient will react to very small amounts of A. If large doses are given there results a serious condition in which the above symptoms are exaggerated.

As in the tests on animals, the therapeutic results on the human being were first obtained with preparations of A containing about 4 to 5 per cent. of iodin. Later they were repeated, using the purer form of the compound that contained 25 per cent. of iodin, and, finally, the typical effects with the same severity were obtained by using the pure crystalline compound containing 60 per cent. of iodin.

These results brought out a great difference in the sensitiveness of dog and man to the toxic iodin compound. To produce effects in dogs, about 1 mg. of A iodin per kilogram weight of dog is required for a daily dose. In the human being severe symptoms follow the administration of as little as $\frac{1}{75}$ to $\frac{1}{25}$ of 1 mg. per bodyweight per day. Furthermore, the nervous system seems to respond much more quickly and strongly in the human being than in the dog. Why the minimum dose required to produce toxic effects in people varies greatly is now being investigated.

In this connection it is interesting to recall the argument put forward that the iodin compound in the thyroid was not necessary for physiological activity, as the thyroid of the fetus and infants contains little or no iodin,[13] [14] a point which has been well reviewed by Hunt.[7] Fenger[15] has recently shown that with proper technic the presence of iodin can be demonstrated in the thyroid of the fetus, and the results reported in this paper show why so little is present. If a daily dose of $\frac{1}{4}$ of 1 mg. is too much for a seven-year-old cretin, weighing 20 kilos, it is readily seen that the thyroid of a 3 to 5 kilos fetus need not contain a very large amount of iodin to maintain the normal function of the gland.

In addition to observations on the pulse rate and general condition, electrocardiograms were taken of several cases. The results obtained were very marked and surprising, and while the number

of cases is not large, they seem to justify a preliminary report at this time.

No interpretation is given for the changes occurring in the cardiograms, as they are among a number which were taken in a preliminary study to see whether the cardiograph could be used as an aid in establishing the action of A and B preparations. In every case there was a change which appeared by slow and regular steps,

FIG. 1.—Crystals of the iodin-containing compound which occurs in the thyroid.

so that a series taken on fourteen or twenty-one successive days showed a great difference between the first and last, but the change between any two days was hardly noticeable.

The cardiograms were all taken under uniform conditions. Unfortunately the instrument was standardized without the patient in circuit, the tension of the fiber being such that .001 volt produced a difflection of 2 cm. The resistance of the patient was not taken.

Since the fiber was standardized without the patient in circuit no certain interpretation can be given for the changes, but there are only two possible explanations: either the body resistance was

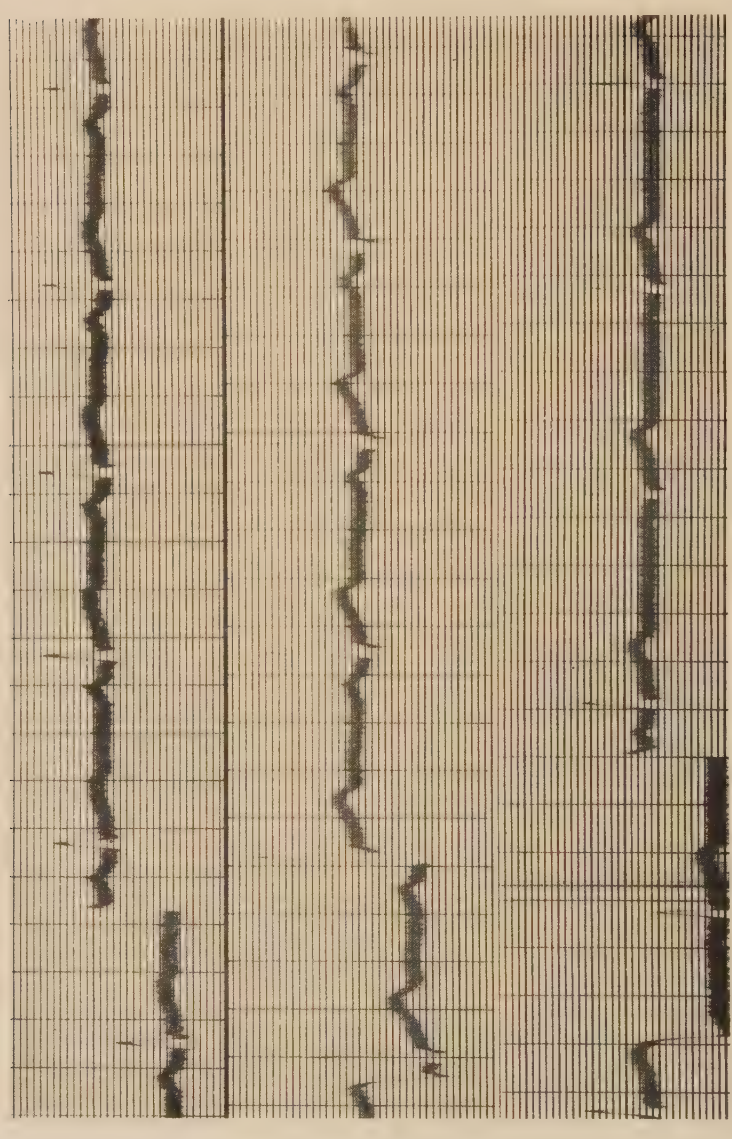

FIG. 2.—Cardiogram of normal man on entering clinic. Pulserate, 75. Body resistance: 1st lead, 5000 ohms; 2d lead, 7000 ohms; 3d lead, 7000 ohms.

greatly reduced, and hence the fiber was more strongly affected, or else a greater electric impulse was produced by the heart beat.

The following three cardiograms shown were taken with the

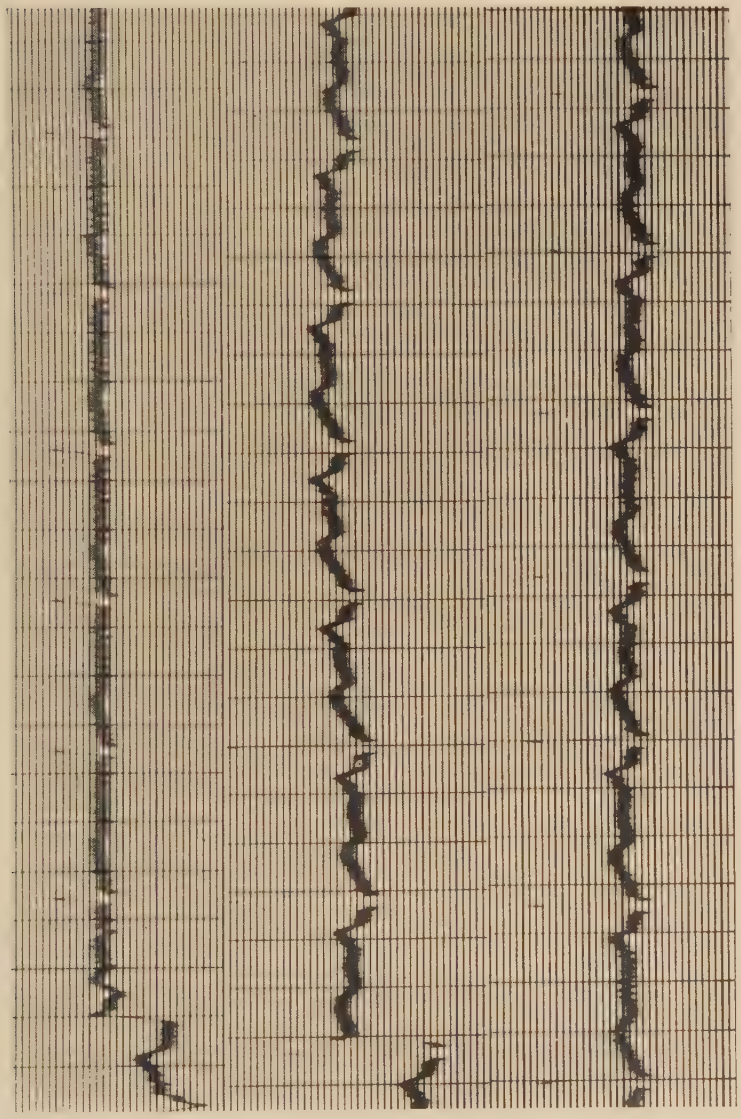

FIG. 3.—Cardiogram of same patient after taking A-iodin for two days. Daily dose, 3 mg. Pulse rate, 90. Body resistance: 1st lead, 6900 ohms; 2d lead, 5900 ohms; 3d lead, 6900 ohms.

fiber standardized to such a tension that 1 mvt, produced a change of 1 cm., the patient being in circuit. The resistance of the patient was determined in every case. These three cardiograms, which are

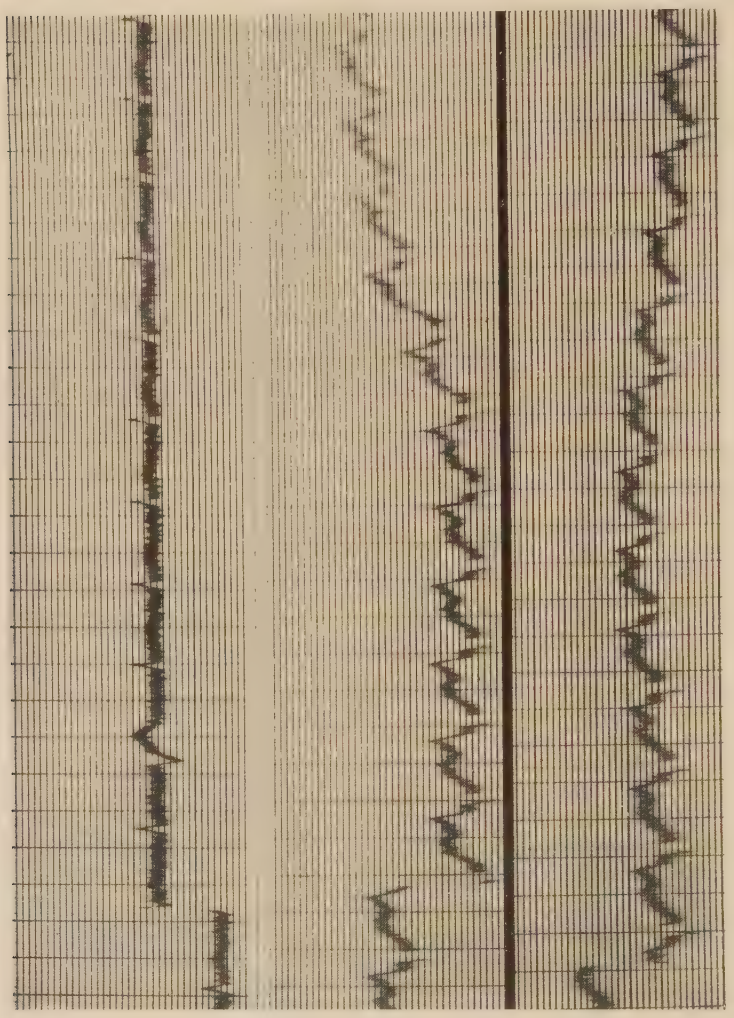

FIG. 4.—Cardiogram of same patient after taking A-iodin for two weeks. Total amount taken, 61 mg. Pulse rate, 144. Body resistance: 1st lead, 2250 ohms; 2d lead, 2500 ohms; 3d lead, 1250 ohms.

from a series of eighteen taken on successive days, indicate that still, under these conditions, there are changes in the various waves of the cardiogram as well as in the pulse rate. A more detailed study of these changes is now being carried out (Figs. 2, 3, and 4).

Effect of A and B on Growth and Mental Activity. It has long been known that the growth of cretins is materially influenced by administration of desiccated thyroid. It was therefore interesting to determine the effects of A and B in this respect. A cretin, aged nine years, weight 16.8 kilos, height 93 cm., was given B alone for ten weeks. Observations on her pulse rate, weight, and height showed no appreciable change during this period, although certain other conditions, which are discussed later, were relieved. At the end of the ten weeks a small amount of A (0.5 mg. A iodin) was included in the daily dose. As there was a rapid response, the pulse rate increasing to 140, the dose was reduced to $\frac{1}{3}$ mg. of A iodin per day, and this amount was continued for six months. Her weight and height were taken on the following dates:

Dates.	Weight. kilos.	Height. cm.°
January 4, 1915	16.30	92.5*
January 27, 1915	16.10	95.0
February 27, 1915	16.70	95.0
April 2, 1915	17.30	97.5
May 5, 1915	16.90	97.5
June 24, 1915	17.10	99.5
July 8, 1915	18.60	102.0

Although no apparent effect was produced with the B constituents in respect to growth, administration of A-iodin was followed by rapid and continued increase. At the same time the mentality was markedly improved. Formerly she was phlegmatic, not easily aroused, did not play with other children, and was backward in talking. She has greatly changed in appearance, manners, and desire to play and talk (Figs. 5 and 6).

In this case so little A iodin was given that no toxic symptoms were produced and only a tonic effect resulted. The cretin is abnormal because of the absence of something. This deficiency can apparently be supplied by the administration of very small amounts ($\frac{1}{180}$ grain per day) of the A iodin compound.

Another case similar to this one in respect to the effect on the mentality was observed with an adult suffering from myxedema.

* The observations on January 4 and July 8 were taken at our Clinic. The other measurements were made at the home of the patient.

For six months this patient was treated with B alone. At the end of that time, although entirely relieved of subjective symptoms, she was still greatly troubled with inability to keep awake. She

FIG. 5.—Cretin as she appeared on entering clinic. Patient had never been treated with any thyroid preparation. Aged nine years; height, 93 cm.; weight, 17.3 kilos.

Fig. 6.—Same patient eight months after Fig. 5. During this time patient was given the A-iodin compound. Helght, 102 cm.; weight, 18.6 kilos.

FIG. 7.—Patient with myxedema on entering hospital.

FIG. 8.—Same patient after six weeks' treatment with A and B. Patient lost twenty-five pounds, was relieved of many subjective symptoms, and regained her naturally bright mentality.

would fall asleep in street cars, while resting on a park bench, etc., and had great difficulty in remaining awake even a few hours a day. When in this condition, small daily doses of A produced immediate and striking relief. Within a few days the patient's whole appearance changed, her naturally bright and witty personality was fully restored, and the desire for sleep was reduced to normal (Figs. 7 and 8).

Does the Thyroid Contain More than One Physiologically Active Substance? This question cannot be definitely answered at this time, but there is evidence that at least one other substance besides the compound containing A iodin produces physiological effects under certain conditions. The acid-soluble group of constituents, designated B, produces no apparent effect when given to normal dog or man, but certain symptoms of myxedema and some conditions of the skin appear to be relieved by the administration of B alone. The symptoms in myxedema relieved by B alone are burning sensations of the skin, with smarting, itching areas, soreness of bones and joints, and cramps of the muscles. No stress is laid on the relief of these symptoms, but they are mentioned in the possibility of drawing attention to the condition in other cases. They are present only in the more severe types of myxedema.

Also, a dry, scaly skin with absence of perspiration in cases not diagnosed myxedema is relieved by B alone. Engman[16] has treated a number of such cases, and among them two patients suffering from dermatitis exfoliativa. In practically all cases improvement has been noted, and in no case have there been any toxic symptoms produced. At our clinic, 92 cases have been treated with B constituents, and in no case have there been any toxic effects noticed. Twelve cases of cretinism and mongols have been treated over thirty days with large doses of B. Pulse rate, respiration, temperature, and weight were taken for the entire period. While there were individual variations the average results showed no apparent toxic effects.

This non-toxic effect of the B group of constituents is in strong contrast with the A group, since they both contain iodin. The iodin-containing compound in A has been isolated and its toxicity shown; the iodin in B is in organic combination, but the nucleus

to which it is attached is unknown and no relation of iodin to activity is evident. We do know that the compound containing iodin in B is not the same substance as the compound containing iodin in A, but whether B iodin and A iodin exist independently in the gland or whether B iodin is a decomposition product from the iodin-containing compound of the A group is still unknown. By the same reasoning, whether the physiological activity of B is simply altered A, by which alteration its toxicity is removed but its activity is not entirely destroyed, or whether there are two or more separate compounds existing independently in the gland, has not yet been proved. (Chart II.)

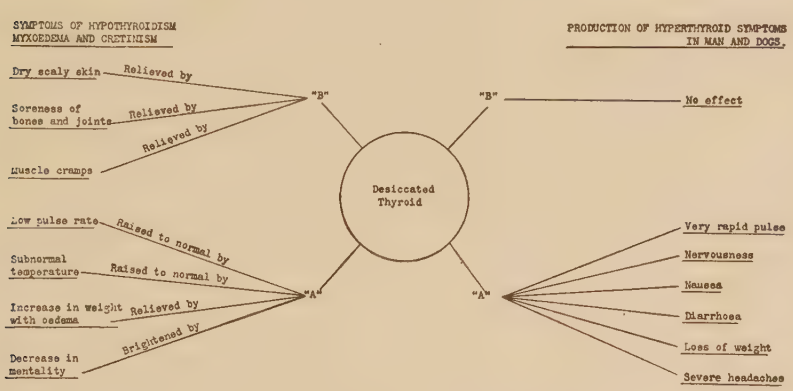

CHART II.—Relation between physiological activity and chemical constituents of the thyroid.

Plummer[17] gives the clinical aspects of excessive activity of the thyroid as follows:

"All of the associated facts make it seem highly probable that the syndrome accompanying hyperplastic thyroid is in the main directly attributable to excessive thyroid function. Assuming this to be true, we can in a general way point out the action of the product of this activity.

"The effect of small doses continued over a relatively short time is cerebral excitation, vasomotor dilatation, rise in blood-pressure, stimulation of the heart, and general metabolism. Moderate doses cause cerebral irritability, mental and muscular incoördination, free perspiration, loss of weight and strength, and cardiac insuf-

ficiency. Large doses exaggerate the preceding effects, mental depression follows cerebral irritability, vomiting and nausea result from a dose but little short of fatal. Relatively small doses continued over a long period give rise to the evidence of more permanent types of damage, such as cardiac arrhythmia, cardiac fibrillation, hypertension, etc.

"Most of the variations in the course and severity of this clinical syndrome can be explained by an equation, taking into consideration the size of the dose, the length of its administration, the general and local susceptibility of the individual to the toxin. This conception in no way invalidates the possibility of an anti-toxic action, relation of the thyroid to other ductless glands, more or less perversion of the thyroid secretions, etc."

At the present time there are no satisfactory means of recording, in a quantitative way, the degree of nervous irritability or the increased cerebral activity produced by administration of thyroid preparations. It is possible, therefore, to record only those changes which are expressed in terms of measurable quantities, the pulse rate, weight, temperature, and nitrogen elimination, but changes in these factors are accompanied by many other effects which to the observer are as striking and as important. The tables following contain the records of several experiments on animals and observations on patients, but the mere tabulation of pulse rates cannot convey an adequate or comprehensive picture of the changes in any case. An increase in the pulse rate of A. J. G. from 86 to 144 was accompanied by headaches, loss of appetite, and a distinct tremor, with dyspnea, but no quantitative record could show these other symptoms.

Effect on Dogs of Administering A Containing about 5 Per Cent. of Iodin

TABLE I.—A-IODIN INJECTED SUBCUTANEOUSLY, 1 MG. PER KILO BODYWEIGHT

Date.	Pulse.	Temperature, centigrade.	Weight, kilograms.	Appetite.	Treatment.
June 23, 1914	116	38.9	11.12	..	All following injections subcutaneous.
June 24, 1914	110	37.9	11.12	1	
June 25, 1914	110	38.0	11.12	1	
June 26, 1914	110	38.0	11.12	1	
June 27, 1914	102	37.8	10.91	1	
June 28, 1914	106	37.8	10.91	1	
June 29, 1914	106	37.9	10.45	1	
June 30, 1914	102	37.9	10.45	1	
July 1, 1914	102	37.9	10.59	1	
July 2, 1914	102	37.9	10.59	1	
July 3, 1914	106	37.8	10.59	1	
July 4, 1914	...	....	10.59	1	
July 5, 1914	108	37.9	10.68	1	
July 6, 1914	106	37.9	10.59	1	
July 7, 1914	...	....	10.59	1	
July 8, 1914	108	37.9	10.45	1	
July 9, 1914	116	38.5	10.22	½	10.4 mg. A-iodin.
July 10, 1914	142	38.8	10.22	1	10.4 mg. A-iodin.
July 11, 1914	136	38.8	10.00	1	10.4 mg. A-iodin.
July 12, 1914	136	39.0	10.00	1	10.4 mg. A-iodin.
July 13, 1914	220	39.2	10.15	1	10.4 mg. A-iodin.
July 14, 1914	250	38.8	10.00	1	
July 15, 1914	144	38.9	9.65	1	
July 16, 1914	126	38.9	9.85	1	
July 17, 1914	126	38.5	9.85	1	
July 18, 1914	110	38.4	10.00	¼	
July 19, 1914	114	....	10.00	½	
July 20, 1914	130	38.9	10.00	¼	
July 21, 1914	125	38.7	9.85	1	
July 22, 1914	118	38.7	10.15	1	
July 23, 1914	116	38.5	10.30	1	
July 24, 1914	116	37.8	10.28	1	
July 25, 1914	116	38.0	10.45	1	
July 26, 1914	...	....	.....	1	
July 27, 1914	108	38.1	10.68	¾	
July 28, 1914	100	38.3	10.45	¼	
July 29, 1914	96	38.0	10.22	1	
July 30, 1914	96	37.9	10.22	1	
July 31, 1914	92	37.8	10.30	1	
August 1, 1914	92	38.3	10.22	¾	

Diet, 200 grams dog biscuit per day.

Appetite judged on scale of 0 to 1 according to food eaten. The entire day's ration was offered to the dog but once every day, the portion not eaten within ten to fifteen minutes was removed.

Effect of Injection of A Containing but Little Iodin; of B Iodin and of Potassium Iodide

TABLE II.—A FROM SHEEP THYROID CONTAINING VERY LITTLE IODIN

Date.	Pulse.	Temperature, centigrade.	Weight, kilograms.	Appetite.	Treatment.
July 16, 1914	100	38.7	10.00	0	
July 17, 1914	96	38.2	9.88	¼	
July 18, 1914	126	38.1	9.68	½	
July 19, 1914	120				
July 20, 1914	118	38.2	10.00	¼	
July 21, 1914	118	37.9	9.88	1	400 mg. of A from sheep thyroid containing 0.16 mg. I.
July 22, 1914	102	38.3	10.10	1	400 mg. of A from sheep thyroid containing 0.16 mg. I.
July 23, 1914	110	38.4	10.00	¾	400 mg. of A from sheep thyroid containing 0.16 mg. I.
July 24, 1914	106	38.4	10.00	1	400 mg. of A from sheep thyroid containing 0.16 mg. I.
July 25, 1914	114	38.8	9.88	1	400 mg. of A from sheep thyroid containing 0.16 mg. I.
July 26, 1914	132	....	.....	1	400 mg. of A from sheep thyroid containing 0.16 mg. I.
July 27, 1914	118	39.0	10.25	1	
July 28, 1914	110	39.2	10.10	1	
July 29, 1914	120	39.0	10.25	1	
July 30, 1914	120	38.3	10.30	1	
July 31, 1914	118	37.9	10.25	1	
August 1, 1914	110	38.0	10.25	1	

Diet, 200 grams of dog biscuit per day.

No apparent effect was produced after injection of A from sheep thyroids very low in iodin. The dog did not develop any other apparent symptoms, as nervousness or tremor.

TABLE III.—A FROM COLLOID GOITRES CONTAINING VERY LITTLE IODIN

Date.	Pulse.	Temperature, centigrade.	Weight, kilograms.	Appetite.	Treatment.
July 16, 1914	132	38.5	5.91	¼	
July 17, 1914	120	38.5	5.62	¾	
July 18, 1914	120	39.5	5.91	1	
July 19, 1914	120				
July 20, 1914	120	39.3	6.02	1	
July 21, 1914	120	38.5	5.91	1	200 mg. A from colloid goitres, 0.5 mg. iodin per day.
July 22, 1914	120	38.9	6.12	1	200 mg. A from colloid goitres, 0.5 mg. iodin per day.
July 23, 1914	108	39.0	6.20	1	200 mg. A from colloid goitres, 0.5 mg. iodin per day.
July 24, 1914	106	38.4	5.80	1	200 mg. A from colloid goitres, 0.5 mg. iodin per day.
July 25, 1914	118	38.9	5.80	1	200 mg. A from colloid goitres, 0.5 mg. iodin per day.
July 26, 1914	120	....	....	1	200 mg. A from colloid goitres, 0.5 mg. iodin per day.
July 27, 1914	118	39.0	6.12	1	
July 28, 1914	120	39.0	5.98	½	
July 29, 1914	102	38.8	6.02	¾	
July 30, 1914	116	38.7	6.22	1	
July 31, 1914	104	38.9	6.28	1	
August 1, 1914	104	38.7	6.22	1	
August 2, 1914	104	....	5.98	1	
August 3, 1914	104	....	6.12	1	
August 4, 1914	104	....	6.22	1	
August 5, 1914	104	....	6.22	1	
August 6, 1914	106	....	6.28	1	
August 7, 1914	118				
August 8, 1914	108	....	....	1	
August 9, 1914	...	....	....	1	
August 10, 1914	102	....	6.22	1	
August 11, 1914	106	....	.....	1	
August 12, 1914	102	....	5.98	1	
August 13, 1914					
August 14, 1914	100				
August 15, 1914	106	....	6.02		
August 16, 1914					
August 17, 1914	100	....	6.02	1	
August 18, 1914	106	....	6.08	1	12 mg. A-iodin.
August 19, 1914	116	38.8	6.02	1	12 mg. A-iodin.
August 20, 1914	150	38.8	5.98	½	12 mg. A-iodin.
August 21, 1914	160	38.9	5.91	1	12 mg. A-iodin.

Diet, 120 grams of dog biscuit per day.

Similar to Table VII, except A, from colloid goitres low in iodin was used instead of A from sheep thyroid. A subsequent injection of 12 mg. of A iodin caused the typical increase in pulse rate and other symptoms.

TABLE IV.—B-IODIN, 1 MG. PER KILO BODYWEIGHT. LATER A-IODIN, 1 MG. PER KILO BODYWEIGHT

Date.	Pulse.	Temperature, centigrade.	Weight, kilograms.	Appetite.	Treatment.
June 23, 1914	106	38.4	7.28	0	All following injections given subcutaneously.
June 24, 1914	110	38.6	7.28	1	
June 25, 1914	115	38.5	7.28	1	
June 26, 1914	126	39.5	7.45	1	
June 27, 1914	114	38.8	7.40	1	
June 28, 1914	116	38.9	7.40	1	
June 29, 1914	116	38.8	7.15	1	7.35 mg. B-iodin.
June 30, 1914	122	38.3	6.81	1	7.35 mg. B-iodin.
July 1, 1914	128	39.2	6.81	1	7.35 mg. B-iodin.
July 2, 1914	123	38.7	6.81	¼	7.35 mg. B-iodin.
July 3, 1914	123	38.9	6.70	½	7.35 mg. B-iodin.
July 4, 1914	126	38.4	6.60	1	7.35 mg. B-iodin.
July 5, 1914	123	38.5	6.60	½	7.35 mg. B-iodin.
July 6, 1914	126	39.0	6.70	½	7.35 mg. B-iodin.
July 7, 1914	128	38.9	6.60	1	7.35 mg. B-iodin.
July 8, 1914	126	38.9	6.70	1	7.35 mg. B-iodin.
July 9, 1914	123	39.1	6.92	1	
July 10, 1914	123	38.8	6.85	1	
July 11, 1914	120	39.1	7.05	1	
July 12, 1914	126	39.1	7.05	1	
July 13, 1914	126	39.0	7.05	1	
July 14, 1914	110	39.0	6.92	¼	
July 15, 1914	110	38.9	7.05	1	
July 16, 1914	110	38.8	7.05	1	
July 17, 1914	110	38.8	7.05	1	
July 18, 1914	110	38.9	6.92	1	
July 19, 1914	110				
July 20, 1914	118	39.2	7.15	1	
July 21, 1914	116	38.9	7.15	1	
July 22, 1914	120	38.9	7.15	1	7.35 mg. A-iodin.
July 23, 1914	132	38.4	7.28	1	7.35 mg. A-iodin.
July 24, 1914	140	38.4	7.28	1	7.35 mg. A-iodin.
July 25, 1914	146	39.1	6.81	1	7.35 mg. A-iodin.
July 26, 1914	156	....	6.81	1	7.35 mg. A-iodin.
July 27, 1914	186	39.4	7.15	¾	7.35 mg. A-iodin.
July 28, 1914	160	39.5	6.81	¼	7.35 mg. A-iodin.
July 29, 1914	164	39.6	6.92	1	7.35 mg. A-iodin.
July 30, 1914	150	38.9	6.81	1	7.35 mg. A-iodin.
July 31, 1914	152	38.9	6.81	1	7.35 mg. A-iodin.
August 1, 1914	148	39.0	6.70	1	
August 2, 1914	148	....	6.70	1	
August 3, 1914	144	....	6.48	¾	
August 4, 1914	126	....	6.65	1	
August 5, 1914	132	....	6.81	1	
August 6, 1914	126	....	6.81	1	
August 7, 1914	118	....	6.81	1	
August 8, 1914	108	....	6.92	1	
August 9, 1914	...	....	6.85	1	
August 10, 1914	108	....	6.85	1	

Diet 128 grams dog biscuit daily.

Injection of B iodin 1 mg. per kilo did not cause any appreciable change in pulse rate or produce nervous symptoms. A subsequent injection of A iodin, using the same amount per kilo, produced the typical effects.

TABLE V.—IODIN IN FORM OF POTASSIUM IODIDE, 5 MG. PER KILO

Date.	Pulse.	Temperature, centigrade.	Weight, kilograms.	Appetite.	Treatment.
September 9, 1914	120	38.4	5.70	1	
September 10, 1914	118	....	....	1	30 mg. iodin as KI
September 11, 1914	120	38.4	....	1	30 mg. iodin as KI
September 12, 1914	114	....	5.50	1	30 mg. iodin as KI
September 13, 1914	114	....	5.35	1	30 mg. iodin as KI
September 14, 1914	108	38.5	5.35	1	30 mg. iodin as KI
September 15, 1914	90	38.9	5.25	1	30 mg. iodin as KI
September 16, 1914	100	....	5.25	1	30 mg. iodin as KI
September 17, 1914	90	....	5.25		

Injections of potassium iodid in amount six times as large as is necessary to produce toxic symptoms with A iodin caused no apparent change.

TABLE VI.—EFFECT OF INJECTION OF THE COMPOUND IN A CONTAINING IODIN, PARTIALLY PURIFIED. IODIN CONTENT 25 PER CENT.

Date.	Pulse.	Temperature, centigrade.	Weight, kilograms.	Appetite.	Treatment.
December 7, 1914	107	38.9	8.64	0	
December 8, 1914	107	38.8	8.64	$\frac{3}{4}$	
December 9, 1914	107	38.8	8.64	$\frac{1}{4}$	25 mg. A-iodin.
December 10, 1914	124	39.0	8.41	$\frac{1}{2}$	25 mg. A-iodin.
December 11, 1914	160–80	39.2	8.30	$\frac{2}{3}$	
December 12, 1914	142	39.3	8.30	$\frac{2}{3}$	
December 13, 1914	150	39.3	8.18	$\frac{1}{2}$	
December 14, 1914	154	39.1	8.18	$\frac{2}{3}$	
December 15, 1914					
December 16, 1914	135	39.1	8.18	$\frac{1}{2}$	
December 17, 1914	120	38.9	8.18	$\frac{2}{3}$	
December 18, 1914	110	39.1	8.18	$\frac{2}{3}$	

Diet, 170 grams of dog biscuit per day.

Typical effects were produced by this A purified until its iodin content was 25 per cent.

Effect of Injection of the Compound in A Containing Iodin Purified to a Single Crystalline Compound with a Constant Iodin Content of 60 Per cent.

TABLE VII.—CRYSTALLINE COMPOUND CONTAINING 60 PER CENT. OF IODIN, ISOLATED FROM A. WEIGHT OF DOG, 6.35 KILOS

Date.	Pulse.	Treatment.
January 11, 1915	110	
January 12, 1915	110	20 mg. A-iodin crystals.
January 13, 1915	130	20 mg. A-iodin crystals.
January 14, 1915	160	20 mg. A-iodin crystals.
January 15, 1915	167–176	
January 16, 1915		
January 17, 1915	196	
January 18, 1915	195–210	
January 19, 1915	156–176	
January 20, 1915	134–162	
January 21, 1915	150	
January 22, 1915	134	
January 23, 1915	140	
January 24, 1915		
January 25, 1915		
January 26, 1915		
January 27, 1915	150	

The same typical effects on pulse rate and nervous symptoms followed injection of the pure crystalline compound isolated from A.

The following tables show changes in the pulse rate of patients after taking group A constituents in various stages of purity up to and including the crystalline form of the compound containing iodin:

Effect of administering group A constituents containing 5 per cent. of iodin.

TABLE VIII.—MRS. W. APPARENTLY NORMAL. WEIGHT 103 KILOS. AGED FORTY-FIVE YEARS

Date.	Pulse rate.	Amount of A iodin per day.
November 13, 1914	86	Total amount 152 mg.
November 16, 1914	120	From November 13 to November 23, 5 mg.
November 19, 1914	137	
November 20, 1914	131	
November 23, 1914	140	From November 23 to November 25, 4 mg.
November 24, 1914	141	
November 25, 1914	135	From November 25 to November 30, 8 mg.
November 27, 1914	130	
November 28, 1914	150	
November 30, 1914	150	From November 30 to December 2, 9 mg.
December 1, 1914	141	
December 2, 1914	142	From December 2 to December 5, 12 mg.
December 3, 1914	143	
December 4, 1914	142	

During this time, although the patient had rapid pulse, loss of appetite, and became nervous and dyspneic, the weight was but little affected.

Effect of administering group A constituents containing 25 per cent. of A iodin.

TABLE IX.—A. J. G., MALE, NORMAL WEIGHT 60 KILOS, AGED THIRTY-EIGHT YEARS

Date.	Pulse rate.	Amount of A iodin per day.
May 29, 1915	86	From May 29 to June 7, 3 mg.
May 31, 1915	96	
June 1, 1915	114	
June 2, 1915	100	
June 3, 1915	114	
June 4, 1915	117	
June 5, 1915	120	
June 7, 1915	120	From June 7 to June 13, 6 mg.
June 8, 1915	122	Total amount 61 mg.
June 9, 1915	125	
June 10, 1915	130	
June 11, 1915	130	
June 12, 1915	138	
June 12, 1915	144	
June 14, 1915	144	

Effect of administering pure crystalline compound isolated from group A constituents.

TABLE X.—F. B., FEMALE, CRETIN, WEIGHT 15 KILOS, AGED SIX YEARS

Date.	Pulse rate.	Amount of iodin.
March 5, 1915	124	
March 6, 1915	106	
March 8, 1915	117	
March 9, 1915	117	
March 10, 1915	120	
March 11, 1915	117	From March 11 to March 25, 0.5 mg. of A iodin per day.
March 12, 1915	120	
March 13, 1915	117	Total amount 7 mg. A iodin.
March 14, 1915	120	
March 15, 1915	123	
March 16, 1915	123	
March 17, 1915	126	
March 18, 1915	120	
March 19, 1915	126	
March 20, 1915	128	
March 22, 1915	140	
March 23, 1915	133	
March 24, 1915	142	
March 25, 1915	142	
March 26, 1915	140	

This cretin had not previously been treated with thyroid.

SUMMARY. 1. By an alkaline alcoholic hydrolysis the thyroid proteins are broken into many simpler constituents, which by their solubility in acids are separated into two groups. Those constituents insoluble in acid are designated group A and those soluble, group B. No definite crystalline compound has been isolated from group B, but it appears to be composed of mixtures of amino-acid complexes. About one-half the total iodin in the thyroid proteins appears among the group B constituents. The nucleus to which the iodin is attached is unknown.

By continued hydrolysis the group A compounds have been further separated and the iodin-containing compound has been isolated in pure crystalline form, having a constant iodin content of 60 per cent. Its exact formula cannot now be given, but its chemical properties are best expressed by di-iodo-di-hydroxy-indol.

2. Physiological tests on dogs and human beings have shown that no toxic effects can be produced by any of the constituents of group B. Group A constituents, however, produce the so-called hyperthyroid symptoms; increase in pulse rate, with tachycardia, increase of nitrogen elimination, with loss of weight, and increase in nervous irritability, etc. Further investigation showed that the production of these symptoms was proportional to the iodin content, that partial purification of A did not destroy the activity, and finally that the compound containing A iodin produced these effects in all stages of purity up to and including the pure crystalline form.

3. The amount of the A iodin compound necessary to produce symptoms is extremely small. One-half milligram ($\frac{1}{120}$ of a grain) per day produced marked effects in a cretin weighing 15 kilos. The susceptibility of animals and man to this compound varies greatly, but the human being responds much quicker and to a far greater degree than the dog. Some form of tolerance for the compound is produced.

In very small doses the A iodin compound exerts a tonic effect, and appears to be essential for normal growth and life.

4. Administration of A iodin to man produces changes in the cardiogram.

5. Although B produces no toxic effects, it appears to possess physiological properties in cases of myxedema and certain con-

ditions of the skin. Whether there are two or more active constitutents in the thyroid, or whether the activity of B is due to minute traces of A, or to A which has been altered so that its toxicity is destroyed, but not its activity, are questions which are under investigation.

The toxic properties of A are due to the iodin-containing compound which has been isolated. There appears to be no relation between activity and iodin in B.

During the course of this investigation I have become indebted to Dr. F. C. Wood, director of the pathological department, St. Luke's Hospital, New York City; to Dr. C. B. Cauldwell of Lincoln, Illinois, and to Dr. M. F. Engman, of St. Louis, for clinical observations. In the Mayo Clinic, I wish to thank especially Dr. C. H. Mayo, Dr. H. S. Plummer, and Dr. L. B. Wilson for the opportunity to carry out the investigation and for encouragement, advice, and help during the work.

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DISCUSSION

Dr. L. F. Barker: Nothing could be more striking than the effect of the compound isolated by Dr. Kendall upon the electrocardiographic tracings. In the myxedema cases, the low, slow excitation waves gave place, in a most remarkable way under the influence of this substance, to strong excitation waves. The curves thus experimentally produced resemble closely the electrocardiograms seen in Graves' disease, and these, in turn, as has for some time been known, are very much like those yielded by normal hearts after vigorous bodily exercise.

Dr. Henry A. Christian: I would like to ask the reader whether body resistance was measured when the various electrocardiograms were taken and whether the curves were standardized on this basis? The tissue resistance in the myxedema cases it seems to me must be taken into account in considering the electrocardiograms; the stronger excitation waves after the administration of the newly isolated compound may be due to differences in resistance in the myxedematous and the improved states, rather tham to changes in the heart itself.

Dr. Edward C. Kendall: There can be no doubt about the specificity of the action of this substance on the heart. There have been a great number of observations: for seven days no change is to be observed, then gradually the effect of the drug on the heart becomes manifest. The increased excursions to be noted in the electrocardiograms may be due to diminished body resistance as Dr. Christian suggested; this is a factor that needs to be taken into account.

BLOOD-PRESSURE AND THYROTOXICOSIS

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In a paper presented before this Association two years ago, the term "thyrotoxicosis" was applied to the constitutional state or states that may be associated with goitre. It was not my intention to include such definite pictures of hypothyroidism as myxedema and cretinism. Sufficient evidence was presented to demonstrate that exophthalmic goitre is a definite clinical entity always associated with hyperplastic thyroid. To show this relationship, and for the reason that no definite relationship can be established between the various other pathologic pictures found in the thyroid and the constitutional states accompanying them, the following classification was tentatively used: (1) hyperplastic toxic; (2) hyperplastic atoxic; (3) non-hyperplastic toxic; (4) non-hyperplastic atoxic.

Of the patients coming to operation, approximately 32 per cent. are hyperplastic and 68 per cent. non-hyperplastic.

Of the patients having hyperplastic goitre, 99.2 per cent. have toxic symptoms and 0.8 of 1 per cent. are atoxic. Very small areas of hypertrophy and hyperplasia are disregarded in this classification. Of the patients having non-hyperplastic goitre, from 20 per cent. to 32 per cent. are toxic and from 68 per cent. to 80 per cent. atoxic.

The onset of exophthalmic goitre is relatively acute and the course of the disease fairly definite. The order of onset of the more important symptoms, based on the average of our series, is as follows: (1) mental excitation; (2) vasomotor disturbances; (3) tremor; (4) mental irritability; (5) tachycardia; (6) loss of strength;

(7) cardiac insufficiency; (8) exophthalmos; (9) loss of weight; (10) diarrhea; (11) vomiting; (12) mental depression.

All of the associated facts make it seem probable that the syndrome accompanying hyperplastic thyroid is, in the main, attributable to a toxin in some way associated with a perverted, deficient or excessive thyroid function. Assuming an over-activity, we can for the purpose of associating our observations, in a general way point out the action of the product of this activity. The effect of small doses continued over a relatively short time is cerebral excitation, vasomotor dilatation, rise in systolic blood-pressure, stimulation of the heart, and general metabolism. Moderate doses cause cerebral irritability, mental and muscular incoördination, free perspiration, loss of weight, loss of strength, and cardiac insufficiency. Large doses exaggerate the preceding effects, mental depression follows cerebral irritability, vomiting and nausea result from a dose but little short of fatal. Relatively small doses continued over a longer period give rise to the evidence of more permanent types of damage, such as auricular fibrillation, hypertension, etc.

The degree of acute intoxication is indicated by the symptoms directly attributable to the nervous system, and the cardiac damage is, in a broad way, indicative of the degree of chronic intoxication.

Assuming the same toxin to be active in non-hyperplastic toxic goitre, still smaller doses acting over a longer period, may, without evidence of acute intoxication, lead to myocardial degeneration. The history and findings may not materially differ from that of myocardial damage arising from other toxins. May a smaller dose insufficient to cause either symptoms of acute intoxication or myocardial insufficiency lead to a cardiovascular syndrome with high blood-pressure and untimately to a true arterial hypertension?

Most of the variations in the course and severity of thyrotoxicosis can be conceived on an equation, the factors of which are: the dose of the toxin, the length of its administration and the general and local susceptibility of the individual to the toxin. This conception in no way invalidates the possibility of an antitoxic action, relation of the thyroid to other ductless glands, more or less perversion of the thyroid secretion, etc.

Patients coming to operation with non-hyperplastic toxic goitre give a history of having first noticed the goitre at the average age of twenty-two years and the evidence of intoxication at the average age of 36.5 years. The corresponding ages for hyperplastic goitre are respectively 32 and 32.9 years. Eliminating the cases in which there is definite reason for thinking that the hyperplasia was ingrafted on a preceding non-hyperplastic goitre, the average interval is only 3.5 months.

More than half of these patients in our Clinic come under observation within a year after the onset of the symptoms. If the average course of the intoxication be represented by a curve, the greatest height is reached during the latter half of the first year.

Considered in the aggregate, hyperplastic goitre develops rapidly, leads to an intense intoxication, accompanied by marked disturbance of the nervous system and cardiac damage.

On the other hand, toxic symptoms develop in cases having non-hyperplastic thyroid only after the elapse of fourteen and a half years (average). Myocardial damage on the whole dominates the fully developed clinical picture. In a small percentage of cases the intoxication is of sufficient intensity to produce a syndrome simulating that of early mild, or atypical, but never that of frank fully developed exophthalmic goitre.

In 63 of the 916 cases of non-hyperplastic goitre coming to operation in 1914, an enlarged heart with low blood-pressure was noted. In at least 50 per cent. of these cases, considered individually, there was but little evidence to suggest thyroid intoxication, except the associated goitre.

Many patients give a history dating back three, four, or more years to an indefinite onset of loss of strength, loss of weight, palpitation, etc., terminating in the evidence of cardiac incompetency that brings them to the Clinic for the resection of a goitre first noted twenty years before. Occasionally a severe thyrotoxic syndrome develops suddenly, as it were, from the dumping of a stored-up toxin into the circulation. It is not my purpose to go into the various phases and types of thyroid intoxication, further than to lead up to the suggestion that the non-hyperplastic thyroid may possibly be in some way associated with a chronic intoxi-

cation, and that the toxic agent may be active for years preceding the condition that we recognize as thyrotoxicosis. From this it is but a step to the conception that a still lower degree of intoxication might in the course of years lead to a cardiovascular syndrome with hypertension.

TABLE I.—AVERAGE BLOOD-PRESSURE BY HALF DECADES; NON-HYPERPLASTIC GOITRE

Years.	Number of cases.	Average systolic blood-pressure.	Average diastolic blood-pressure.
10 to 15	15	118.5	72.5
15 to 20	63	120.7	77.7
20 to 25	128	123.1	80.2
25 to 30	190	123.8	80.5
30 to 35	235	126.9	81.2
35 to 40	253	134.9	83.6
40 to 45	246	136.4	85.2
45 to 50	214	145.8	87.3
50 to 55	204	150.2	87.1
55 to 60	131	152.6	87.5
60 to 65	47	160.7	88.6
65 to 70	13	164.6	83.3
70 to 75	4	166.2	87.5
75 to 80	2	106.0	65.0

TABLE II.—AVERAGE BLOOD-PRESSURE BY HALF DECADES; HYPERPLASTIC GOITRE

Years.	Number of cases.	Average systolic blood-pressure.	Average diastolic blood-pressure.
10 to 15	14	138.5	68.8
15 to 20	58	139.4	75.9
20 to 25	110	137.8	70.7
25 to 30	164	139.6	75.2
30 to 35	139	140.8	78.7
35 to 40	106	155.2	75.6
40 to 45	93	145.1	76.7
45 to 50	94	153.1	77.8
50 to 55	47	152.4	77.0
55 to 60	17	160.6	77.7
60 to 65	5	160.0	71.2
65 to 70	0	000.0	00.0

TABLE III.—PERCENTAGE OF CASES OVER FORTY YEARS OF AGE HAVING HIGH BLOOD-PRESSURE

	Number of cases.	Systolic blood-pressure above 150	Systolic blood-pressure above 160
Hyperplastic goitre	117	47	34
Non-hyperplastic goitre	417	35	27
Cholecystitis with stones	289	..	18
Uterine myoma	100	25	15
Positive Wassermann	100	21	14

The average high systolic blood-pressure attending hyperplastic goitre is shown in Tables II, III, and IV. The high pulse-pressure with the well known vasomotor phenomena in exophthalmic goitre leads to the almost unquestionable conclusion that there is no vascular hypertension in this condition. The high systolic pressure is essential to the maintenance of a normal diastolic blood-pressure in these cases having a low peripheral resistance. In many cases even a normal diastolic pressure is not maintained. That the long-continued intoxication associated with the hyperplastic thyroid may lead to hypertension is probable. Evidence to show this will not be considered in this paper. On the other hand, an unduly open peripheral vascular system is occasionally present in patients recovered from exophthalmic goitre. The height of the systolic blood-pressure in exophthalmic goitre is somewhat indicative of the degree of intoxication.

Table II, giving the average blood-pressure readings for non-hyperplastic goitre cases by half decades, at once demonstrates the association of high systolic blood-pressure with this condition, unless there are in the series many cases in which the association of the goitre and the high blood-pressure is accidental. To be further assured of the association of high blood-pressure with non-hyperplastic goitre, the percentage of cases over forty years of age having a systolic blood-pressure above 160 was compiled for hyperplastic goitre, non-hyperplastic goitre, cholecystitis with stones, uterine myoma and syphilis, conditions all tending to produce high blood-pressure.

Table IV shows the percentage of cases from the second to the sixth decade having systolic blood-pressure above 160. The average blood-pressure and percentages given in this paper, except those in Tables I and II, include only the cases operated upon in 1914. The figures compiled for 1912 and 1913 cases on which this paper was originally based, do not materially differ.[1]

[1] They are not published here as they were not compiled on quite the same basis and are not comparable without confusing explanation, and the 1914 statistics are more accurate. I will not encumber the paper with any discussion regarding the accuracy of the statistics, further than to state that there may be an occasional high reading which would be much more than offset in the tables giving percentages by the inclusion of the non-operated cases having high blood-pressure.

TABLE IV.—SHOWING PERCENTAGE OF CASES BY DECADES, HAVING A BLOOD-PRESSURE ABOVE 160

Age.	Age, 10 to 20 years. Per cent.	Age, 30 to 40 years. Per cent.	Age, 30 to 40 years. Per cent.	Age, 40 to 50 years. Per cent.	Age, 50 to 60 years. Per cent.	Age, 60 to 70 years. Per cent.
Hyperplastic goitre . .	12	17	22	30	37	300
Non-hyperplastic goitre	1	2	7	21	• 31	· 20

That 27 per cent. of patients having non-hyperplastic goitre above forty years of age are accompanied by a systolic blood-pressure above 160, eliminates the question of an accidental association. This question has been checked by much data, the publication of which is unnecessary. Is this high percentage of cases having a high systolic blood-pressure due to the inclusion in this series of a large number of non-hyperplastic goitres accompanied by acute intoxication?

Further consideration of the relation of high blood-pressure to non-hyperplastic goitre is facilitated by grouping the cases of non-hyperplastic goitre coming to operation in 1914 as follows:

Group I. Symptomatically negative, systolic blood-pressure, below 160, 582 cases.

Group II. Symptomatically positive, systolic blood-pressure, below 160, 224 cases.

Group III. Symptomatically negative, systolic blood-pressure, above 160, 36 cases.

Group IV. Symptomatically positive, systolic blood-pressure, above 160, 74 cases.

Group I includes the cases in which there is little if any evidence of disturbed thyroid function. The average systolic blood-pressure, however, is high for the patients over thirty-five.

Group II includes the cases having a systolic blood-pressure below 160 diagnosed as toxic non-hyperplastic goitre. In this group are to be found many cases that some diagnosticians would include with the exophthalmic goitres.

Group III symptomatically negative, systolic blood-pressure above 160. These cases came under observation without any notable complaint except the presence of the goitre. The findings in these cases range from little more than the high systolic blood-pressure to those of a well-developed cardiorenal syndrome.

Group IV, symptomatically positive, systolic blood-pressure above 160. While many of the cases in this group are markedly thyrotoxic, this can be excluded and the symptoms definitely attributed to the high blood-pressure, cardiovascular or cardio-renal syndrome, in 37.

Including the 37 cases in Group IV with Group III, systolic blood-pressures above 160 were noted without any tangible evidence of thyrotoxicosis in 18.1 per cent. of all cases over forty years of age. This percentage seems to definitely establish the association of high systolic blood-pressure with non-hyperplastic goitre, unaccompanied by definite evidence of thyrotoxicosis.

Of the 110 cases having a systolic blood-pressure of over 160, 30 had a diastolic blood-pressure above 105. While it may not be true of individual cases, there can be no doubt that this group with high diastolic readings has more or less permanent cardiovascular damage. What the relation may be between these cases and the cases having relatively low, diastolic blood-pressure and a high systolic blood-pressure we have not sufficient evidence to answer. It was my purpose to present in this paper much evidence that seems to suggest that the high systolic blood-pressures, though often transitory, are due to the same factors that later lead to high diastolic blood-pressure and permanent cardiovascular changes. This leads into so complete an analysis of the material that I have found it impossible to handle the necesary statistical matter in time for publication in this paper.

I wish to again call attention to the fact that the clinical syndromes associated with hyperplastic and non-hyperplastic goitre are, for the purpose of this article, in the main, attributed to the products of an over-active thyroid only as a convenient hypothesis. The establishment of exophthalmic goitre as a definite entity associated with hyperplastic thyroid (Plummer); the rise and fall in the clinical evidence of intoxication corresponding with the development and regression of the hyperplasia (Wilson); and the separation of a pure chemical compound from the thyroid (Kendall), having a physiological action closely in line with that assumed for thyrotoxicosis; almost, if not fully, warrant accepting this assumption as an established fact for hyperplastic toxic goitre. (It is probable

that all hyperplastic goitres are delivering a product above the normal.) The consideration of the clinical picture in all its aspects alone leaves but little room for doubt. That the same or a modified product is in some way associated with the thyrotoxicosis of non-hyperplastic goitre is almost equally well established. The facts suggest that the hyperplastic thyroid is constantly delivering this product into the circulation while they offer the theory that the non-hyperplastic goitre may, relative to the demands, either retain or deliver its product, the periods of overdelivery leading to thyrotoxicosis.

If we associate the arterial hypertension with non-hyperplastic goitre the problem becomes more complex, and it is perhaps best to stop with the conception that the thyroid is not properly performing its function. Returning to facts, I wish to emphasize the point that I have left open the question of the association of arterial hypertension and goitre.

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THE RELATIONSHIP OF THE PATHOLOGICAL HISTOLOGY AND THE IODIN COMPOUNDS OF THE HUMAN THYROID

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The present study presents some new evidence in the solution of the problems of the relationships between the clinical, pathological, and chemical findings in cases of human goitre. The scope of the study is limited to 566 cases, from which specimens have been analyzed chemically in the course of a general investigation of the iodin compounds of the thyroid. The cases were not selected but were taken at random in the order as operated on, from the patients under treatment in the Mayo Clinic during 1914.

Clinical Classification. The clinical classification of the cases into (1) hyperplastic toxic ("exophthalmic" goitre); (2) non-hyperplastic toxic, with high blood-pressure; (3) non-hyperplastic toxic, with low blood-pressure; (4) non-hyperplastic questionably toxic, with low blood-pressure, and (5) non-hyperplastic atoxic, with low blood-pressure has been made by Plummer,[1 2] and follows his previous grouping. Though the terms "hyperplastic" and "non-hyperplastic" refer to the morphology of the gland, which cannot be shown until its removal, yet they have been used in making the clinical diagnoses by Plummer and his associates with but a negligible margin of error as shown by the subsequent pathological examination.

Pathological Classification. The pathological classification is, with slight modification, that previously published by

Wilson.[3 10] The main divisions, (1) primary hypertrophy and hyperplasia of epithelium; (2) primary retention of colloid with atrophy of epithelium; (3) encapsulated adenomas, and (4) carcinomas, with their several subdivisions, are self-explanatory. As our study of the morphology of the thyroid in goitre has progressed, it has been found desirable to subdivide the group of regressing hyperplasias into subgroups, early, advanced and very advanced regression. Also the undegenerated, encapsulated adenomas, with small or undeveloped acini, group E, and the undegenerated, encapsulated adenomas with colloid-filled acini, group G, are so few in proportion to the degenerated adenomas, group F, that in the present study the three subgroups have not been separated. The encapsulated adenomas have been separated from adenomatoses, and the latter included in the group described as primary retention of colloid with atrophy of epithelium.

Chemical Investigation. The methods employed in the determination of iodin and the dry weight of thyroid substance removed at operation were as follows:

The fresh gland was placed in a crystallizing dish, covered with a glass plate, and heated three or four hours in an oven at 100° C. This preliminary treatment removed a large portion of the water and made the gland cut more easily into smaller pieces. After the gland was cut into small pieces, it was completely dried in a vacuum desiccator, and then ground to a fine powder in a coffee mill, thoroughly mixed, and the iodin content determined[11] in a one-half gram portion. Two modifications of this procedure were employed for some of the glands. Instead of taking the entire fresh gland for purposes of desiccation, a known portion of the total was taken, and from the dried weight of this portion the dried weight of the total gland and the amount of iodin were calculated. The other modification consisted in taking a portion of the gland after it had been fixed in 4 per cent. formaldehyd. From this known portion the dried weight of the total gland was determined, and the total iodin based on this weight. Analysis of the formaldehyd solution showed that in every case an appreciable amount of iodin from the gland had passed into the formaldehyd solution. It was therefore necessary to determine the amount of

iodin in this solution to obtain the total iodin originally present in the portion of the gland removed at operation. The results obtained by these procedures were kept separate until after they were compared with the pathological grouping. This comparison showed no appreciable differences between the three methods, so that in the final tabulation of results there was no discrimination made as to which method was employed for determining the total dried weight and the total iodin.

In addition to the determination of the total iodin, the dried thyroid substance of fifty-eight thyroids was hydrolized by a method already published.[13] This hydrolysis splits the proteins into simpler products and divides the total iodin into two chemically different groups. The α-iodin compound is insoluble in acids. The β-iodin compound is soluble. Both α- and β-iodin are in organic combinations and there is evidence that β-iodin is not a decomposition product of the α-iodin compound but that the two forms exist independently in the gland. Physiological tests[14] have shown that the α-iodin compound produces the typical effects of desiccated thyroid, but that the β-iodin compound has no toxic action. It therefore seemed desirable to determine the amount of α-, or toxic, iodin compound in some of the glands removed. For the determination of the amount of α-iodin in a given gland, the dry powdered gland was boiled in 90 per cent. alcohol in the presence of 1 per cent. sodium hydroxid for forty-eight hours, 2.5 grams of the dried thyroid per 100 c.c. of alcohol. At the end of the boiling, carbon dioxid was passed through the solution and the alcohol evaporated. The solution was then acidified with 20 per cent. sulphuric acid. The precipitate (α-constituents) was filtered and washed with a small amount of water. This precipitate was dissolved in sodium hydroxid. The amounts of iodin in the filtrate (β-constituents) and in the solution of the α-constituents were determined. This gave the amounts of α- and β-iodin, and the sum of these two the total iodin in the gland.

In connection with the determination of iodin, it may be said that the results obtained during the course of this investigation approximate 4000 determinations of iodin. From a comparison of duplicates and an inspection of the accuracy of the total series,

it would appear that for this work the method used is entirely adequate. The great advantage of obtaining a perfect "blank" where no iodin exists, of having no blue color flashed back from the starch iodin reaction after titration is finished, and the wide range in the amounts of iodin which come within the method, together with the shortness of time and inexpensive chemicals, have made this method the one of choice in our laboratory.

Protocols. The bulk of the material makes publication of protocols obviously cumbersome. However, the protocols of the chemical analyses and pathological examinations, with the microscopic sections, gross specimens and the clinical histories are on file in the Mayo Clinic, and are open to study by anyone interested. The results have been accurately compiled and condensed into a series of tables herewith presented.

Discussion of Tables. *Table I.* The distribution of the cases into the several clinical and pathological groups is given in totals, rather than in averages, that the numbers may serve as a basis for determining the percentage values in subsequent comparisons. It will be observed that the number of cases in certain groups (*A*, hyperplastic toxic; *D*, non-hyperplastic toxic and non-hyperplastic questionably toxic; *H—F*, non-hyperplastic toxic and non-hyperplastic questionably toxic; *F*, questionably toxic; and the carcinomas) are so small as to make the averages of relatively little value. However, it would have been more inaccurate to omit these cases entirely, and attention will be called to the insufficient evidence presented in these groups as the several comparative tables are discussed later. It should be noted that of the 425 cases of non-hyperplastic goitre, 197 presented symptoms which might have caused many of them to be diagnosed as "exophthalmic goitres" by clinicians elsewhere. Without analyzing in detail the distribution of these cases, it may be pointed out that the general distribution closely approximates that shown in a similar group of patients operated on in 1911 and 1912.[9]

Table II. This shows the average age of the patients at the time their thyroids were removed. While the average age of the patients with hyperplastic toxic goitre is thirty-five years, it will be noted that the average age of those with early hypertrophy

GOITRES, CORRELATION OF PATHOLOGICAL, CLINICAL AND CHEMICAL DATA

Pathological Classification.	Clinical Classification.	Table I.—Number of Cases.						Table II.—Average Ages (in Years).					
		1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).	1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).
1. Primary Hypertrophy and Hyperplasia of Epithelium:													
A. Early hypertrophy and hyperplasia		2	..	..	..	..	2	19	..	..	..	..	19
B. Advanced hyperplasia		44	..	..	..	..	44	34	..	..	..	..	34
C 1. Early regression of hyperplasia		38	..	..	..	..	38	38	..	..	..	..	38
C 2. Advanced regression of hyperplasia		36	..	..	..	..	36	35	..	..	..	..	35
C 3. Very advanced regression of hyperplasia		17	..	..	..	..	17	34	..	..	..	..	34
2. Primary Retention of Colloid; Atrophy of Epithelium:													
D. Secondary regeneration of epithelium		4	16	5	4	25	54	29	45	40	33	32	32
H. Diffuse atrophy of epithelium		..	65	35	11	96	207	..	50	37	35	35	40
H + F. Diffuse atrophy of epithelium with included adenomas		..	27	9	2	47	85	..	49	33	38	36	40
3. Encapsulated Adenomas:													
E, F, G		..	25	12	7	35	79	..	46	40	44	36	40
4. Carcinomas		..	3	—	—	1	4	..	44	—	—	42	44
Totals (average)		141	136	61	24	204	566	35	49	38	38	35	39

is only nineteen years, of those with advanced hyperplasia thirty-four years, and of those whose thyroids showed regression in the hyperplastic process it is thirty-eight, thirty-five and thirty-four years respectively, in inverse order to the amount of regression. At first thought it would appear that this inversion of the average ages in relation to the amount of regression of hyperplasia is contradictory, but when the average ages are examined in the light of Table III, in which is shown the average duration of goitre in months, it will be seen that while the younger patients showed the greatest amount of epithelial regression the duration of the goitre as well as the duration of symptoms were both also inversely as to age and directly as to the amount of regression. The same holds good in the four cases of clinically hyperplastic toxic goitre with secondary regeneration of the thyroid epithelium. Here the average age was twenty-nine years, and though the average duration of goitre was one hundred and thirty-two months, the average duration of symptoms was only eleven months. In this pathological group (epithelial regenerations), the age-distribution of the patients in the various clinical classes is interesting, being twenty-nine years in the hyperplastic toxic, forty-five years in the non-hyperplastic toxic with high blood-pressure, forty years in the non-hyperplastic toxics with low blood-pressure, thirty-three years in the non-hyperplastic questionably toxic, and thirty-two years in the non-hyperplastic atoxic cases.

The somewhat erratic age distribution of the cases in which the glands showed encapsulated adenomas, either alone (*E*, *F*, *G*) or included in diffuse colloid goitres (*H*+*F*), may not be wholly accidental, but may be due to the influence of the neoplasms. This point, however, is still under investigation in a larger series of cases.

Table III. The average duration of goitres in months for the entire series and the duration of hyperthyroidism in months for the hyperplastic series is shown in Table III. The duration of the symptoms in the toxic non-hyperplastic cases is so difficult to determine with any degree of accuracy from the patient's description that no attempt has been made to state it in months. The difference between the period of duration of goitre in hyperplastic toxics,

GOITRES, CORRELATION OF PATHOLOGICAL, CLINICAL AND CHEMICAL DATA

TABLE III.—AVERAGE DURATION OF GOITRES AND AVERAGE DURATION OF TOXIC SYMPTOMS (IN MONTHS).

PATHOLOGICAL CLASSIFICATION.	CLINICAL CLASSIFICATION. 1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).
PRIMARY HYPERTROPHY AND HYPERPLASIA OF EPITHELIUM:						
A. Early hypertrophy and hyperplasia	9 (9)	..	..	..	..	9 (9)
B. Advanced hyperplasia	17 (10)	..	..	..	..	17 (10)
C 1. Early regression of hyperplasia	32 (18)	..	..	..	..	32 (18)
C 2. Advanced regression of hyperplasia	53 (35)	..	..	..	..	53 (35)
C 3. Very advanced regression of hyperplasia	68 (47)	..	..	..	..	68 (47)
PRIMARY RETENTION OF COLLOID; ATROPHY OF EPITHELIUM:						
D. Secondary regeneration of epithelium	132 (11)	216	276	204	156	209
H. Diffuse atrophy of epithelium	..	240	180	240	168	204
H + F. Diffuse atrophy of epithelium with included adenomas	..	216	156	240	168	180
3. ENCAPSULATED ADENOMAS:						
E, F, G	..	180	180	192	156	168
4. CARCINOMAS	..	192	—	—	300	252
Totals (averages)	41	228	180	216	168	

TABLE IV.—AVERAGE SYSTOLIC BLOOD-PRESSURE.

1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).
140	..	..	..	..	140
138	..	..	..	..	138
147	..	..	..	..	147
132	..	..	..	..	132
144	..	..	..	..	144
148	164	129	120	125	140
..	171	130	128	120	141
..	176	121	132	124	143
..	171	129	126	128	144
..	157	—	—	120	142
143	171	128	127	123	

averaging forty-one months, and the period of duration of goitre in the non-hyperplastic groups (the lowest of which is 156 months, and the highest 276 months, with an average of 192 months), is very marked, and constitutes a point in clinical diagnosis.

The maximum severity of symptoms, and the severity at the time of examinations in the several groups of hyperplastic toxic cases, indicated on a scale of 1, 2, 3, 4, and 5, averaged as follows:

	Maximum severity.	At time of examination.
A. Early hypertrophy	1.0	1.0
B. Advanced hyperplasia	2.6	2.5
C 1. Early regression	3.2	2.4
C 2. Advanced regression	3.6	2.5
C 3. Very advanced regression	3.4	2.0

Table IV. The discussion of the systolic blood-pressure as presented in Table IV will be covered *in extenso* by Plummer.[16] It is included in the present paper only for reference in relation to the percentage of iodin and total amount of iodin in the portion of removed gland. (See Tables VI and VII.)

Table V. The average weight of the portion of the gland removed at operation in the hyperplastic toxic group was 57 grams, as compared with 55 grams, the average weight of the removed portion in the 1911 and 1912 cases.[9] The average weight of the removed portion of the 425 cases of non-hyperplastic thyroids was 168 grams, as compared with 171 grams, the average weight of the non-hyperplastics in the 1911 and 1912 series.[9] This is of significance in showing the great disparity in size between the thyroids from hyperplastic toxic and those from non-hyperplastic toxic cases as previously noted.[3 9] In the individual groups the removed portion of gland is larger in the cases of high blood-pressure than in the several pathological groups with low blood-pressure.

Table VI. The variation in the percentage of iodin in the dried gland in the several histological types of thyroids from hyperplastic toxic cases is most marked. Starting in with the cases of early hypertrophy, the percentage is 0.11. It drops thence to 0.03 in the advanced hyperplasias, rises to 0.07 in the early regressions, to 0.16 in the advanced regressions, and to 0.19 in the very advanced regressions. A comparison of these percentages with those showing

TABLE V.—AVERAGE WEIGHT OF REMOVED GLAND (FRESH) IN GRAMS.

TABLE VI.—AVERAGE PER CENT. OF IODIN IN DRIED THYROID.

PATHOLOGICAL CLASSIFICATION.	CLINICAL CLASSIFICATION. 1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).	1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastictoxic (?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).
1. PRIMARY HYPERTROPHY AND HYPERPLASIA OF EPITHELIUM:												
A. Early hypertrophy and hyperplasia	46	..	..	..	..	46	0.11	..	..	..	..	0.11
B. Advanced hyperplasia	59	..	..	..	..	59	0.03	..	..	..	..	0.03
C 1. Early regression of hyperplasia	56	..	..	..	..	56	0.07	..	..	..	..	0.07
C 2 Advanced regression of hyperplasia	53	..	..	..	..	53	0.16	..	..	..	..	0.16
C 3. Very advanced regression of hyperplasia	70	..	..	..	..	70	0.19	..	..	..	..	0.19
2. PRIMARY RETENTION OF COLLOID ATROPHY OF EPITHELIUM:												
D. Secondary regeneration of epithelium	42	175	146	151	171	159	0.07	0.08	0.14	0.05	0.05	0.07
H. Diffuse atrophy of epithelium	..	223	169	170	158	181	..	0.08−	0.11−	0.08	0.08−	0.08+
H + F. Diffuse atrophy of epithelium with included adenomas	..	189	112	266	183	179	..	0.09	0.12	0.05	0.06	0.07
3. ENCAPSULATED ADENOMAS: E, F, G	..	109	125	140	108	114	..	0.07	0.02	0.04	0.06	0.06
4. CARCINOMAS	..	730	—	—	140	583	..	0.005	—	—	0.07	0.02
Totals (averages)	57	190	150	167	157	137	0.10	0.08	0.10	0.06	0.06+	0.085

percentages of iodin in the various non-hyperplastic thyroids shows that in no subgroup of the latter division, does the percentage of iodin rise as high as that in the thyroids from cases with advanced regression in hyperplastic glands.

In the pathological groups of the non-hyperplastic series the secondary regenerations (type D) present both the highest and the lowest percentages aside from certain low averages in the encapsulated adenomas and the carcinomas. The diffuse epithelial atrophies (type H) vary the least. The encapsulated adenomas while generally low vary from 0.02 to 0.07.

In the individual clinical groups, it is interesting to note that in all, except the adenomas, the percentage of iodin is highest (av. 0.10 per cent.) in the non-hyperplastic toxic cases with low blood-pressure. The next in amount are the cases of non-hyperplastic toxic with high blood-pressure (av. 0.08 per cent.). In general, the percentage is lowest in the non-hyperplastic atoxic (av. 0.06 per cent.). Attention is called to this inversion of the order of the percentage amounts in relation to clinical symptoms over those observed in the cases of hyperplastic goitre.

A tabulation of both groups of non-hyperplastic toxic cases in comparison with the non-hyperplastic atoxic cases shows that in 84 per cent. of the atoxic the percentage of iodin was under 0.1, while but 68 per cent. of the toxic cases was under 0.1.

Table VII. In the hyperplastic toxic cases, the total amount of iodin in the portion of the gland removed follows the percentage of iodin since the portion of gland removed in these cases is fairly equal in the several groups. Thus, the amount averages 9.2 mgs. in early hypertrophy, drops to 3.4 mgs. in the advanced hyperplasias, rises to 8 mgs. in the early regressions, to 14.2 mgs. in the advanced regressions, and to 21.9 mgs. in the very advanced regressions. The total amount in the cases with secondary regeneration of epithelium, which showed symptoms placing them in the hyperplastic toxic clinical group, is the smallest of any of the groups except the advanced hyperplastic toxics and carcinomas.

In the non-hyperplastics, the largest amount is in the toxics with low blood-pressure (23.8 mgs.), while in the atoxics the amount averages 15 mgs. It should be noted that though the amount

of iodin in the portions of glands removed in the non-hyperplastic cases is greater than the amount removed in the hyperplastic cases, the comparison of the relative amounts in the total gland is not made on the same basis since in the non-hyperplastics a very much larger proportion of the gland is removed at operation (frequently as much as $\frac{9}{10}$), than is removed at operation in hyperplastic cases (rarely more than $\frac{2}{3}$).

Thus, it is probable that the total amount of iodin in the entire gland in the cases of hyperplastic goitre with very advanced regression averages more than the total amount of iodin in the entire gland in the non-hyperplastic cases.

The averages of the total iodin of patients grouped as to age by half-decades shows no order or regularity but a similar grouping of the average total amounts of iodin arranged by duration of goitre in half-decades results as follows:

ADDENDUM TO TABLE VII.—TOTAL IODIN AND DURATION OF GOITRE.

Duration of goitre in half-decades.	Non-hyperplastic toxic.		Non-hyperplastic atoxic.	
	Number of cases.	Average total iodin, mgs.	Number of cases.	Average total iodin, mgs.
5−	30	19.6	23	13.7
5+	21	18.4	37	12.3
10+	26	21.3	28	16.9
15+	23	32.9	30	16.9
20+	22	28.3	20	22.5
25+	19	22.3	11	14.0
30+	12	22.1	4	13.5
35+	8	28.3	2	16.2
40+	11	28.3	3	16.0

While there are considerable fluctuations in the total amount of iodin present at the different half-decades the most constant relationship is that at each half-decade the total amount in the toxic cases is materially more than is the total amount in the atoxic cases.

Table VIII. The determination of the α-iodin has been made in too few cases to make the average percentages of much comparative value, there being but 30 cases in the hyperplastic group, and 28 in the non-hyperplastic group. It may, however, be noted that in those groups in which a sufficient number of cases exist for comparison, that the following order is presented: In the cases of advanced hyperplasia, the percentage of the total iodin in the

TABLE VII.—TOTAL IODIN IN PORTION OF GLAND REMOVED (IN MILLIGRAMS).

TABLE VIII.—AVERAGE PERCENTAGE OF α-IODIN (Number of determinations shown in parenthesis).

PATHOLOGICAL CLASSIFICATION.	CLINICAL CLASSIFICATION.	1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).	1. Hyperplastic toxic ("exophthalmic" goitre).	2. Non-hyperplastic toxic with high blood-pressure ("simple" goitre).	3. Non-hyperplastic toxic with low blood-pressure ("simple" goitre).	4. Non-hyperplastic toxic(?) with low blood-pressure ("simple" goitre).	5. Non-hyperplastic atoxic with low blood-pressure ("simple" goitre).	Totals (averages).
1. PRIMARY HYPERTROPHY AND HYPERPLASIA OF EPITHELIUM:													
A. Early hypertrophy and hyperplasia		9.2	..	..	..	..	9.2	7 (1)	..	..	..	..	7 (1)
B. Advanced hyperplasia		3.4	..	..	..	..	3.4	16 (11)	..	..	..	..	16 (11)
C 1. Early regression of hyperplasia		8.0	..	..	..	..	8.0	31 (8)	..	..	..	..	31 (8)
C 2. Advanced regression of hyperplasia		14.2	..	..	..	..	14.2	31 (6)	..	..	..	..	31 (6)
C 3. Very advanced regression of hyperplasia		21.9	..	..	..	..	21.9	37 (4)	..	..	..	..	37 (4)
2. PRIMARY RETENTION OF COLLOID; ATROPHY OF EPITHELIUM:													
D. Secondary regeneration of epithelium		5.7	19.9	25.6	11.9	12.1	14.9	—	—	16 (1)	—	34 (1)	25 (2)
H. Diffuse atrophy of epithelium		..	28.1	32.8	21.1	18.4	23.9	..	30 (2)	33 (4)	38 (1)	35 (6)	34 (13)
H + F. Diffuse atrophy of epithelium with included adenomas		..	27.5	22.2	11.1	13.0	18.6	..	—	25 (1)	—	18 (1)	22 (2)
3. ENCAPSULATED ADENOMAS:													
E, F, G		..	13.8	11.6	6.4	10.0	10.9	..	46 (1)	27 (2)	—	35 (8)	34 (11)
4. CARCINOMAS		..	5.1	—	—	1.6	4.4	..	..	..			
Totals (averages)		9.7	23.8	26.5	14.5	15.0		25 (3)	36 (3)	28 (8)	38 (1)	34 (16)	(58)

α-form is 16 (11 cases), and rises to 35 (18 cases) in the advanced regressions. In the non-hyperplastic cases, if the two groups with toxic symptoms are placed together (11 cases), the average percentage of the total iodin in the α-form is 30, while in the atoxic group (16 cases), the average percentage is 34. Thus it will be seen that there is a parallel relationship in the two groups though until further data is obtained no great significance can be attached to it.

General Discussion. 1. The data herein presented furnishes additional proof of the statements previously made by one of us,[3] that the symptom-complex, which is generally recognized as "typical Graves' disease," "exophthalmic goitre," etc., and sharply denoted by Plummer as hyperplastic toxic goitre, is constantly parallel in all its stages of development and regression with similar stages of development and regression in the parenchyma of the thyroid. This parallelism is shown in the average duration of goitre, the average duration of toxic symptoms, and in the progressive and regressive histological changes.

Now, for the first time in detail, the percentages and total amounts of iodin, the pathological groups and the clinical types have been compared in the same series of cases. As previously suggested by the work of Smith and Broders,[15] a close parallelism obtains throughout the data from the three sources.

From previous investigations there seemed to be little doubt that the clinical picture of exophthalmic goitre is produced, either directly or indirectly, by hyperactivity of the thyroid, but until some definite substance had been isolated from the normal thyroid and from the pathological glands and shown to be toxic in its nature, no final conclusion could be arrived at. The isolation in pure form of a compound containing 60 per cent. of iodin[12 13 14] and the proof that this substance is highly toxic in nature, emphasized the importance of an investigation concerning the amount and nature of the iodin-containing compounds of the thyroid. It has been shown that the iodin in the glands exists in two independent forms of combination, only one of which, the α-form, is toxic. We must therefore enlarge are conception of the physiological action of the iodin compounds to include the action of this one, the toxicity of which is vastly greater than that of any other hitherto described.

It is significant to find that this α-iodin compound is present in the actively hyperplastic glands of advanced hyperplastic toxic goitres in only $\frac{1}{20}$ to $\frac{1}{15}$ the amount in which it is present in normal thyroids. This must be interpreted not as a reduced production of the toxic substance but as the result of its greatly increased diffusion from the gland into the blood stream. There is no quantitative measure of the secretory activity of the thyroid, but its storage capacity for the toxic substance is obviously proportional to its iodin content. If further observations support the relatively few herein recorded, it would seem to be a fair assumption that the α-iodin compound is responsible for the toxic symptoms in hyperplastic toxic goitre. The constant direct relationship between the clinical symptoms and pathological picture and the reservoir capacity of the thyroid in hyperplastic toxic goitre is strikingly shown in Tables VI, VII, and VIII. The failure on the part of other pathologists to recognize this constant association, we believe, has been due, first to failure by clinicians to distinguish sharply between hyperplastic toxic goitre ("typical acute exophthalmic," "Graves' disease," etc.) and the several indeterminate groups of non-hyperplastic toxic goitre ("atypical chronic Graves' disease," "cardiovascular goitre," etc.), and second, failure to recognize the fact long ago suggested,[3] that the chemical constituents found in the thyroid are only the complement of those which must have gone out of the gland to have caused symptoms.

2. The relationships of the pathology and chemistry of non-hyperplastic thyroids to the various clinical groups of toxic and atoxic non-hyperplastic goitre are still far from being cleared up. This is due, (1) to the difficulty in accurately grouping these cases clinically, (2) to the difficulty in securing accurate information as to the onset and course of the chronic symptoms, and (3) to the difficulty in intrepreting long-past primary pathological changes in the light of present pathological and chemical findings, since most of these patients seek surgical aid many years after the beginning of the goitre, and probably also several years after the beginning of symptoms. That the relationship of the histological changes in the thyroids designated as epithelial regenerations is parallel with the iodin content of the glands, and to some extent

with the clinical history of the patients from whom the glands were removed is shown in the several tables.

One fact running through all the tables is that the amount of iodin in the gland parallels the clinical grouping. In the actively hyperplastic glands (group B) it has been shown that the amounts of iodin and α-iodin are very low, but in cases where regression has occurred (group C) the amounts of iodin are high. In contrast to this, it was found that the amount of iodin in the non-hyperplastic toxic glands is higher than in the non-hyperplastic atoxic glands.

The clinical picture, in its most severe type, of patients with non-hyperplastic toxic goitre approaches in many respects the picture of patients with hyperplastic toxic goitre. Assuming the same toxic substance to be the cause for all thyroid intoxication, the factors involved to produce varying clinical pictures, are the daily amount of absorption of the toxic substance, the length of time during which this intoxication occurs, and the personal resistance of the patient. At present we have no conclusive evidence explaining the higher iodin content of toxic non-hyperplastic glands than that of the actively toxic hyperplastic glands, but it seems probable that the diffusibility from the gland of the α-iodin compound may be an important factor in determining whether a goitre produces toxic symptoms or not.

Further rearrangements of the clinical groups of non-hyperplastic goitre are in progress by Plummer, and further studies of the pathology and chemistry of the thyroids from these cases are now being made by us and will be reported later.

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DISCUSSION

Dr. C. F. Hoover: Our experience in Cleveland is in such violent contrast with the conclusions reached in Rochester that I cannot refrain from commenting on the fact. I have gone over many of Marine's preparations and have been able to find no relation whatever between the histology and the clinical histories of the cases.

It may be possible to interpret glands thus in Rochester but no one seems able to do it elsewhere.

I have never seen a case of Basedow's disease with hypertonus; I have never seen a case of Basedow's disease with elevation of diastolic pressure, although usually the systolic shows an elevation to 180.

Dr. Louis B. Wilson: The difference between my conclusions and those of Dr. Marine is largely a difference of classification both of clinical symptoms and of morbid histology. Marine's published studies are based on 69 cases diagnosed clinically as exophthalmic goitre, but many of which we would group clinically as cases with cardiorenal changes developing in the course of simple goitre. Further, I have no doubt that many of the cases which Marine groups histologically as primary hyperplasias, we would group as secondary regenerations. If the clinicians will more clearly differentiate and more accurately group their goitre cases, there will be little difficulty in observing the constant relationship of the histological type of the gland to the clinical manifestations.

A CASE OF PULMONARY MONILIASIS IN THE UNITED STATES[1]

By THOMAS R. BOGGS, M.D.

AND

M. C. PINCOFFS, M.D.

BALTIMORE

Pulmonary mycoses referable to groups of organisms more or less well known to American or European observers have in late years been frequently reported, but so far as the authors are aware no case in which the causative agent was a Monilia has yet appeared in the literature. It therefore seems desirable to make a brief record of this case.

Past History. The patient, a white female, native American housewife, aged forty-four years, was admitted to the City Hospital,[2] Bay View, on January 4, 1915, giving the following history: She had prior to her present illness been normally robust, the only illness of note having been an attack of smallpox at the age of four. She had borne three healthy children, and, in addition to her household duties, had for fifteen years worked each summer in the canning factories. She had no history of previous chronic cough nor other evidence of pulmonary disease.

Present Illness. Early in May, 1914, she applied at a dispensary for treatment on account of what she called a "boil," in the left axilla, which had been present and gradually increasing during three months previous. There was little or no pain, nor had there been any discharge. On examination a tumor was found in the left breast and the diagnosis of mammary carcinoma with axillary metastases was made. The patient refused operation and soon left the city for her usual summer work in the canneries. During

[1] From the Medical Clinic of the City Hospital at Bay View, and the Pathological Department, Johns Hopkins University, Baltimore. The term Moniliasis is tentative as representing our present ideas as to the classification of this organism.

[2] The patient was admitted to the surgical service of Dr. A. M. Shipley, who kindly permitted us to study and report the case.

the latter part of summer she began to notice increasing numbness and tingling in the left hand with some weakness, and a painless swelling of the upper arm. This latter condition continued to increase, so that by early December she was quite incapacitated; the swelling having by this time extended to the breast and the tissues of the chest wall on this side. There was a gradual development of malaise and feverishness. She was admitted to the Johns Hopkins Hospital, December 26, where the diagnosis of mammary carcinoma was confirmed and a large fluctuating axillary abscess was incised and drained. At this time there was no cough or expectoration observed. Four days later she was discharged and told to return for dressings. This she was unable to do, and after five days at home she was admitted to the City Hospital. In this interval she developed a severe cough with profuse expectoration of reddish-gray material.

Physical Examination. On admission the patient seemed very ill; her temperature was 102°, and she was markedly prostrated. She was breathing somewhat rapidly and coughing at frequent intervals. Her tongue was dry and coated with a whitish fur. The mucous membranes of the mouth were not injected and showed no abnormalities. The teeth were in a poor state of preservation: many of them were missing, and those remaining were carious. The pharynx was injected; the tonsils not enlarged. The thorax was somewhat emaciated; the musculature poorly developed and the subcutaneous fat scarce. The left mammary gland was larger than the right and in its lower right quadrant there was a hard irregular mass, neither tender nor painful, and about the size of a hen's egg. It was freely movable over the underlying tissues, and the skin was not adherent to it. The nipple was not retracted and not apparently connected with the mass. The remainder of the gland was of a firmer consistency than normal. The right breast was normal. About 5 cm. from the left arm on the anterior axillary border there was a sinus opening about 1.5 cm. in diameter; the sinus tract extended upward and posteriorly about 4 cm. (Fig. 1). There was a slight sanguineous discharge from it. The infra- and supraclavicular fossæ were obliterated by brawny edema of the tissues, which were reddened and hot to the touch. At the summit of the supraclavicular fossa there was an area of softening and fluctuation. The shoulder and upper arm were diffusely swollen and there was some edema and cyanosis of the forearm and hand. There was great loss of power in the left arm, but no paralysis. The left chest showed marked impairment on percussion, especially over the upper lobe, enfeebled breath sounds, prolonged expiration, and diminished fremitus. There was well-defined cracked-pot resonance below the clavicle and in the supraspinous fossa. A localized friction rub was present in the axilla. The right lung seemed normal on percussion and auscultation. The heart was normal. The radial pulse was smaller on the left. The spleen was not palpable. The abdomen, pelvis, and lower extremities showed nothing further of interest.

Blood: Leukocytes, 13,000; hemaglobin, 60 per cent. (Sahli); Wassermann negative.

Urine: Showed no abnormalities.

The sputum was very abundant, of gruel-like character, odorless, and faintly tinged with blood. On examination between glass plates it was found to contain small grayish masses, from 1 to 2 mm. in diameter, which, when isolated and examined microscopically, contained mycelial threads and yeast-like cells.

FIG. 1.—Photograph five days before death. Sinus and infiltration of left thorax and arm.

After three or four days in the hospital the amount of sputum became somewhat diminished and the cough less frequent. The patient was somnolent; the fever persisted. Five days before her death the discharge from the sinus became profuse and the expectoration almost disappeared. Late on the afternoon of this day a severe hemoptysis took place, with simultaneous small discharge of dark blood from the sinus. After this there was a marked diminution in the cough but the sinus continued to discharge. The patient's weakness became progressively more marked; and on Jan-

uary 17, after a profuse hemorrhage from the sinus, without any hemoptysis, she sank and died in a few moments.

Postmortem Examination. At the autopsy, which was performed three hours after death, the sinus tract was found to arise from two large abscess cavities which lay respectively above and below the clavicle in the upward continuation of the axillary fossa. These intercommunicating cavities still contained considerable purulent material of a reddish-brown tinge. Where these cavities were bounded by the thoracic wall there was evidence

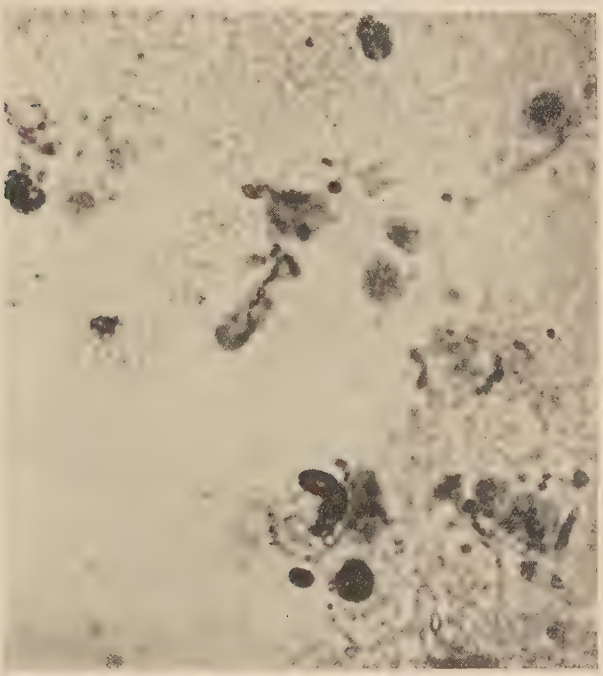

FIG. 2.—Author's cases. Section from clot in bronchus. (*a*) part of filament with coccoid beading; Victoria blue Weigert stain. (× 1000).

that at numerous small points they communicated through the intercostal spaces with the inside of the chest. The intercostal muscles were infiltrated, edematous, and friable. Upon pressure on the chest there appeared at many points, in the intercostal spaces affected, a trickle of the bloody discharge mixed with bubbles of air coming outward through the intercostal musculature, but at no point was a large single communication through the chest wall discovered.

The left breast contained several large nodular masses of firm consistency,

which on section were grayish and translucent on the cut surface, but also showed yellowish, granular areas.

The left thoracic wall was disarticulated at the sternoclavicular notch and the entire chest wall including the lung was peeled out of the skin.

The examination of the left lung and chest wall showed the lung to be bound by dense fibrinous adhesions to the parietal pleura in the upper and posterior third. Particularly at the apex these adhesions were very dense and almost cartilaginous in consistency; in many instances they

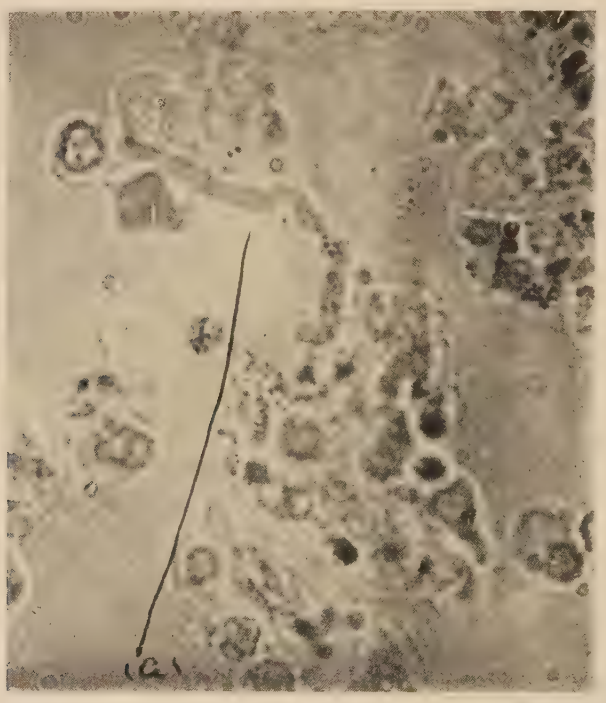

FIG. 3.—Section from pleural exudate. Author's case. Victoria blue Weigert. (× 1000). Showing long cylinder (*a*) and coccoid forms.

were 1 cm. in thickness. The remainder of the lung could be lifted from the chest wall, as it was bound only by delicate adhesions. On palpation the greater part of the upper lobe seemed to be densely consolidated and non-air containing.

A section made through the lung, dividing it in two parts from apex to base, revealed a cavity about 8 cm. in diameter between the two layers of the pleura and just beneath the apex. This cavity contained a large, friable, reddish-brown clot. It was surrounded by a fibrinous wall.

The upper lobe of the lung was consolidated, firm in consistency, gray in color, and with a smooth surface. The remainder of the lung showed areas of similar consolidation growing sparser toward the base, where only a small proportion of the lung was actually involved.

The bronchi, particularly those leading to the upper lobe, contained a reddish-brown coagulum, which was quite friable and in some areas was laminated. The bloodvessels showed no marked abnormality. The glands

FIG. 4.—Author's organism in kidney of rabbit. (× 1000) Toluidine blue stain. Note similarity to Fig. 3.

at the hilus of the lung and in the mediastinum were enlarged and increased in consistency. On section they showed pigmentation and the presence of translucent, grayish areas of infiltration.

The right pleural cavity and the right lung appeared normal.

Little else of interest was found at the autopsy. The reduction in nutrition was evidenced by the scant subcutaneous fat and the atrophic musculature. There was, in all the tissues, evidence of the acute anemia, secondary to hemorrhage. The parenchymatous organs showed moderate

cloudy swelling. Nowhere was there any evidence found of a metastatic extension of the process localized in the left lung, left pleura, and left axillary fossa.

Microscopic Study of Tissue. Sections through the lung show a patchy consolidation, which assumes lobar proportions in the

Fig. 5.—Old culture. Victoria blue. Showing variations in staining. Note coccoid intrahyphal structures (*a*, *a*).

upper lobe. The bronchi are everywhere filled with a cell mass of varying composition consisting in part of pure red-blood cells and in other parts of mixtures of mononuclear cells of polyblastic type and of polynuclear cells. The inflammatory cellular mass involves the walls of the bronchi in many places. These are thickened, only partly fibrosed, and contain many polyblastic cells. At other points the bronchial epithelium is well preserved, showing the

normal ciliation or a metaplasia into several layers of stratified cubical cells.

The exudate in the alveoli varies considerably. For the most part it is poor in nuclei, and is composed of pink-staining, hyaline-like material. This may in places show a filamentous fibrin-like structure; the filaments here and there pass through the pores of Kohn in the alveolar wall. The meshes of this material enclose desquamated cells and small mononuclears; while red-blood cells are uncommon. The alveolar exudate at other points is composed almost wholly of masses of mononuclear and polynuclear cells, with little or no fibrin. The alveolar walls are often broken down in these cell-rich areas. The points of cell-rich exudate grade gradually into the areas in which fibrin-like material predominates.

The pleura is greatly thickened and fibrous. In this inflammatory tissue are found nests of mononuclear and polynuclear cells. This process connects the lung surface with the skeletal muscles, and where the latter are involved evidence of hyaline and waxy degeneration of the fibers and formation of muscle spindles is abundant.

By Weigert's method, in the greater part of the alveolar exudate and some of the pleural exudate, single as well as massed filaments stain intensely and resemble fibrin.

The microscopic demonstration of the organism in this tissue has presented great difficulties as the elements which we have considered to represent the parasite decolorize with almost the same readiness as the surrounding tissue.

With the ordinary Weigert stain under oil-immersion numerous bacteria-like structures are found occurring as single coccoid forms or in chains. The individual elements, however, are not so uniform in size as cocci, are larger, and the chains which they form assume much more tortuous and bizarre shapes. A characteristic picture with this stain is the occurrence of these coccoid bodies in double parallel rows. Here and there filaments may be seen connecting the individual beads in the same row or passing to the opposite side. In other forms the filaments may be more conspicuous and the beads less conspicuous.

A modification of the Weigert stain in which Victoria-blue replaces gentian-violet, seems to give more definite pictures of these

forms and to bring out other related forms which are not seen in the ordinary Weigert stain. These latter are masses appearing sometimes as very long cylinders and sometimes ovoid, about the diameter of a red-blood cell, stained rather deeply blue, and often containing coccoid bodies similar to those described above.

Our impression that the above-described elements are mycelial forms of the parasite is strengthened by a comparison with stained specimens of old cultures. We have frequently noted in smears and sections of old cultures that many of the hyphæ are indicated only by faint shadows, others only by a more or less beaded margin, and still others by wavy cylindrical and ovoid forms with or without granules.

The left breast: Sections through the indurated lump in the left breast revealed diffuse carcinoma.

Cultures from the sputum: The particles from the sputum above described, which contained mycelium, were washed in sterile salt solution, streaked on plates of media in Petri dishes (potato, bread, agar, glucose agar) and observed at room temperature as well as in the thermostat at 37° C. From the potato and agar plates especially, numerous discrete, whitish, moist, glistening, somewhat waxy colonies were obtained. On examination these were found to be made up of yeast-like cells, showing active budding, but no hyphal forms. In addition to these colonies there were a few bacterial colonies, scattered among the various plates. The yeast colonies, however, were present in considerable number on practically every plate and on many in pure culture. This method of culture was repeated with similar results a few days later.

The cultural characteristics of this yeast-like organism were studied in various media, and at different temperatures, both aërobically and anaërobically. It was found to grow luxuriantly on glucose agar, with production of a rather characteristic streak, at first moist, glistening, and opaque, becoming more granular and waxy, with wavy margins and heaped-up centre. There was a marked tendency for the dried out portion to take a brilliant white color, like crumbs of chalk. Litmus-glucose agar was first acidified, becoming slowly alkaline, after eight to ten days. In broth the growth was less abundant, granular, whitish, and always on the

bottom, with clear supernatant fluid and no pellicle. There was fair growth in milk, without acid production, and after three to five weeks a late coagulum developed together with an alkaline reaction. This was a dense uniform coagulum, like soap, and stained deeply blue with the alkaline litmus. There was no fluid expressed by this coagulation. Dextrose and levulose were slowly fermented, with very moderate gas production, which later was almost completely absorbed. There was slight acid production and only a little alcohol. Saccharose, lactose, and mannite were not fermented. There was no indol production in meat broth.

Gelatin was not liquified. Stab cultures in agar and gelatin grew freely in opaque, granular, confluent colonies; showing a good growth even at the bottom of deep stabs: hyphal threads as noted below did not appear in early cultures. In anërobic cultures the production of acid and gas in carbohydrate media was much enfeebled.

The Morphology of the Organism. On the surface of solid media, aërobic and anaërboic cultures grew as yeast-like forms with active budding lateral and terminal. Older cultures began to show a few short threads and oïdial chains, but it was not until the strain had been on media for several weeks and repeatedly transferred that the rapid production of hyphæ and sporulation forms was observed in deep stabs and old fluid cultures. It may be noted also that thread production in all media was more rapid in anaërobic cultures, and when once established it remained constant.

The threads produced in deep stabs and old fluid media were highly refractile, with only a small amount of intercellular substance. Small, free granules (mitochondria ?) with Brownian motion were frequently observed within the hyphæ in fresh preparations. In the surface growth the threads formed were much shorter, and though often jointed, showed little tendency toward branching.

Branching, which is a striking feature in old glucose bouillion and stab cultures, occurs only at the joints by the budding process. Branching may be simple or compound (Figs. 6 to 9); secondary branches arising as the primary ones by budding at the joints. These may show the same phenomena of sporulation as the original

hyphæ do. Sterile hyphæ are frequent and in the stab cultures may occur in tufts.

FIG. 6.—Monilia(?) Author's case. Section × 80 diameters. Fifteen-day gelatin stab. Victoria blue stain. Radial growth of threads and axial spore-clumps Dark masses in centre composed of spores similar in all respects to the axial spores on threads.

The yeast-like cells varied in size from 2.5 to 7 micra in their longest diameter. The smaller forms being very little refractile, filled with protoplasm and indistinguishable from the spores. The

FIG. 7.—Monilia (?) Author's case. Section from eight-day gelatin stab, fuchsin stain. Fruiting hyphæ with lateral and terminal sporulation. (× 1000).

larger showed highly refractile double contoured walls and were vacuolated, with scanty cytoplasm. The hyphal cells varied from 4 to 8 micra in width and in length from a few micra to several millimeters. They were mostly jointed at irregular intervals,

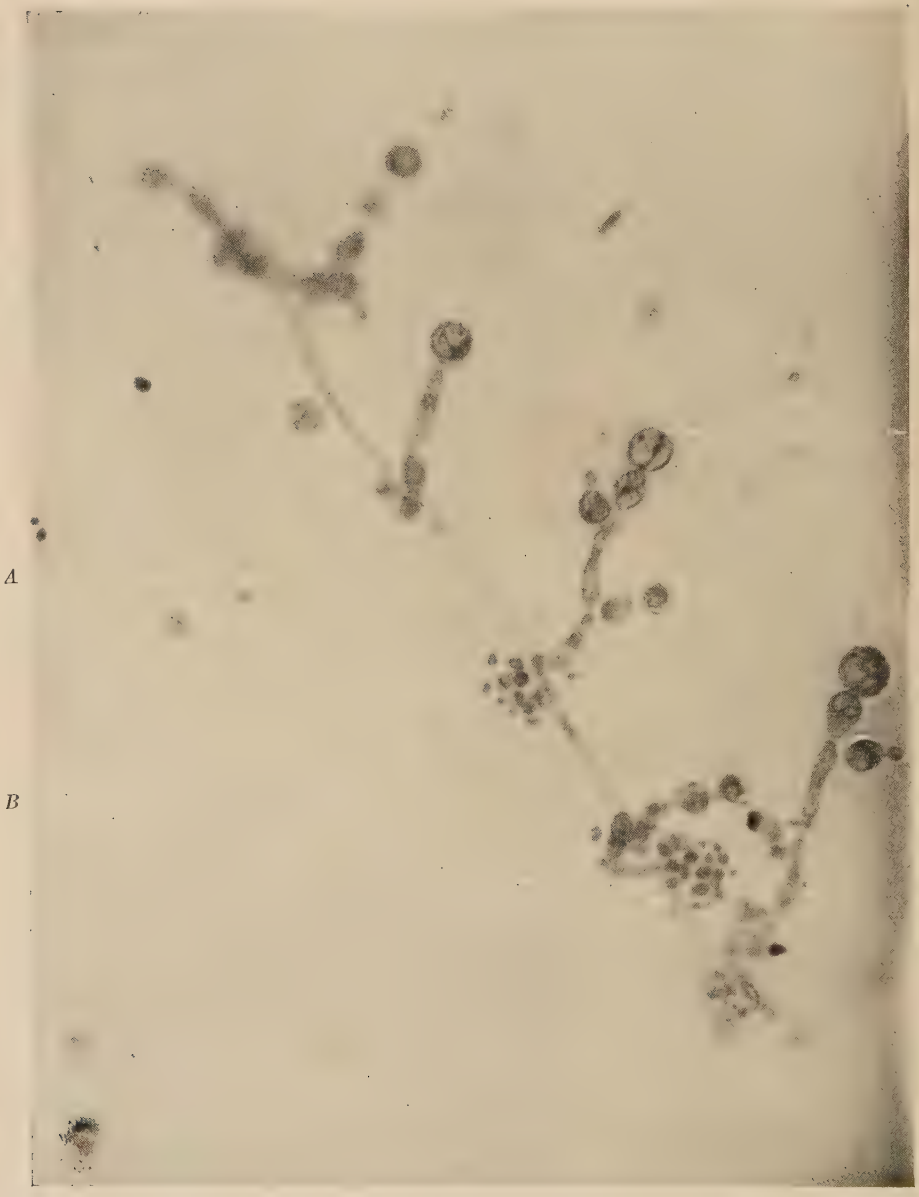

FIG. 8.—Monilia (?) Author's case. Section from eight-day gelatin stab, fuchsin stain. (× 1000). Hypha (*A*) with ordinary spores (*B*) and chlamydospores (*C*) on same thread.

except the sterile hyphæ, which were narrower and often entirely non-septate. No evidence of chromogenesis occurred in any cultures. Smears fixed by heat and stained showed the yeast forms heavily stained without differentiation, while the hyphal cells often were barely tinted or entirely unstained. All the forms were Gram-negative.

Fig. 9.—Endomyces albicans (?) From a child with thrush. Fuchsin stain. (× 500). Radial threads and axial spore-clumps.

The methods of reproduction observed in our cultures were: (1) oïdial chains of spores from large yeast-like cells or hyphæ; (2) lateral masses of free spores without sterigmata which developed by budding at the joints of the hyphæ; (3) terminal sporulation by budding on constriction at the ends of hyphæ. The spores so produced are morphologically like the yeast cells; (4) chlamydospores which may form at the ends of short or long hyphæ, or

singly or in groups at the joint of primary or secondary branches. As to the occurrence of sterigmata we saw none, unless the structures bearing the chlamydospores in Fig. 8 may be so interpreted. Ascosporulation has as yet not been found.

These facts bring the organism in close relation to Monilia candida (Bonorden) and we have adopted the generic name "Monilia" for our organism as distinguishing it from Endomyces albicans which it resembles. Ascosporulation being an accepted determining feature of latter genus. Our Monilia is indistinguishable morphologically from that described by Ashford for tropical sprue.

The best pictures of thread production and sporulation were obtained in stab cultures in 15 per cent. gelatin where the threads grew at right angles through the stab producing a thick, hair-like outgrowth, which occurred at all levels but was best developed just below the surface. The cultures were fixed and hardened in the tube with 10 per cent. formalin, the glass cracked and peeled off, and blocks cut out at any desired level. The blocks were then sectioned with the freezing microtome. These sections were stained in dilute aqueous fuchsin, one-to-thirty, for several hours, and differentiated in saturated acqueous cictric acid until the gelatin was nearly decolorized, then floated on clean slides, air dried without blotting, quickly cleared in xylol and mounted in balsam. For low power study sections stained with aqueous Victoria blue give more brilliant pictures.

These stained sections of stab cultures gave a true picture of the actual relation of the threads and spores as has been described in detail in a previous communication.[1]

Pathogenicity. We found the organism actively pathogenic for rabbits. Intravenous injection produced disseminated lesions in the kidney cortex, intestinal lymph follicles and liver as well as in the striped and unstriped muscles, death occurring in one to eight days. Intratracheal injection in rabbits led to localized pneumonia-like lesions in the lungs with pleurisy and late involvement of other viscera. These animals survived for the most part several weeks. The organism has been recovered in pure culture from the experimental lesions of rabbits.

[1] Johns Hopkins Hos. Bull., 1915, xxvi, 384.

The sections of these lesions show the organism in varying abundance and principally in the form of threads. It is often very difficult to stain the organisms in the tissues, a trait not infrequently observed in mycotic infections. Further studies in the experimental injection of animals are in progress.

We wish especially to acknowledge our indebtedness to Dr. M. C. Winternitz for his constant assistance in the pursuit of the pathological and experimental studies. We are also greatly indebted to Dr. W. W. Ford for the facilities furnished in the study of the cultural characteristics of the organism. Dr. Erwin F. Smith of the Bureau of Plant Pathology, Washington, D. C., and Dr. Admon Clark, Johns Hopkins University, have most kindly made some of the photomicrographs, which we gratefully acknowledge.

DISCUSSION

Dr. Bailey K. Ashford: I was much interested in Dr. Boggs' paper; partly because we encountered a case in which the vagina had been invaded by a monilia, which responded to the complement-fixation test specific for the monilia associated with sprue. We found a suggestive monilia in a carbuncle also.

I have seen only a few cases of pellagra in Porto Rico. I at first took them to be cases of sprue, but no monilia could be found and later erythema and mental symptoms appeared, which settled the matter.

The complement-fixation test remains to be worked out.

STUDIES IN MONILIASIS OF THE DIGESTIVE TRACT IN PORTO RICO

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In April, 1913, I wrote a paper[1] for the Tenth Annual Meeting of the American Society of Tropical Medicine, entitled "Notes on Sprue in Porto Rico, and the Results of Treatment by Yellowed Santonin," announcing the presence of that disease in the island. The paper was the outcome of a clinical study of 86 cases extending over some four years. While the disease, under the name of tropical scurvy or intestinal phthisis, has undoubtedly caused a formidable mortality for many years, of late, perhaps in the last decade, it has made startling advances and has now come to occupy a position in the very front rank of the serious and fatal affections of our island, especially dreaded by American residents among whom it seems to be far more common and fatal than tuberculosis. That it is a disease caused by a specific organism seemed to me likely from the first. The paths most likely to lead to a recognition of that organism seemed: (1) A clinical investigation of the disease, and (2) an epidemiological survey of varied points on the island.

Clinical experience with sprue from the early part of 1909, convinced me that, among other things, it was a separate and distinct clinical entity with four cardinal conditions, sore mouth, excessive intestinal fermentation, light, foamy diarrhea and a diminution in the size of the liver; that it was a chronic affection, with periods of relative health; that no specific had been yet found, nor was any medication comparable to a non-carbohydrate diet, santonin having been found wanting after long and persistent use, and dis-

[1] Am. Jour. of Trop. Dis. and Prevent. Med., 1913, l, 146.

carded in 1913 for emetin which suffered a like fate. In that year the Institute of Tropical Medicine and Hygiene made their annual expedition to the country districts of the interior and fixed the clinical laboratory, hospital and dispensary in a coffee plantation in the mountains of Utuado. We saw in open clinic for all diseases in a period of sixty working days, 10,140 persons, receiving over 36,000 visits. All physicians working with us were instructed to send cases not uncinariasis, as well as cases suffering from complications of that disease, to our special examining room, and as one of the diseases which we were especially seeking in our medical survey was sprue, it is not probable that many cases of it escaped our vigilance. Only 11 cases of complete sprue and 19 doubtful cases were seen, most of them from the town of Utuado. Thus the fact was disclosed that while occasionally found in the rural districts, sprue was really a disease of towns and cities, preferring to take its victims from the higher walks of life rather than from the less sanitary and apparently more exposed poor. For the purpose of contrast, let us consider 25 as the average minimum number of cases of sprue seen each year by physicians in San Juan who are on the watch for it. In this connection let it be said that among these physicians there is little contention over its tendency to present itself in family endemics.

Previously to this expedition, I had concluded that a likely source of infection was bread, rarely consumed by the country laborer, at best intermittently, and a staple in the home in towns. Porto Rican bread was in 1898–1903 a very savory food. Its peculiarly pleasant taste and European style of confection, accredited it to every table. But the bread of Porto Rico has degenerated much in flavor and in confection in the last ten years, complaints of its sourness and soddenness have become more and more frequent, and coincident with this deterioration intestinal fermentative conditions have increased.

Bahr's[1] "Researches on Sprue," was discouragingly received by some of his colleagues, who replied to his modest statement that the circumstantial evidence pointed to *Monilia albicans* as being

[1] Trans. Soc. Trop. Med. and Hyg., April, 1914, vii, No. 5.

the cause of the disease by expressing their inability to accept as a causal agent a fungus common in England where sprue is unknown. At that time I had under my care one of the most typical and, considering the sanitary excellence of his house, one of the most disquieting cases of sprue to American residents which had up to that time claimed public attention. The patient, a young government official, gradually reached the stage of marasmic toxemia, in spite of drugs, trips to the north, and even the classical diet. I sent him north after a partially successful dietetic regime extending over three or four months, and in New York the same diagnosis was independently made by Dr. Crow, U. S. N., who had seen sprue in the East. His return coinciding with the newer ideas of the etiology of sprue, I made three unsuccessful attempts to obtain a growth of yeasts from the denuded but non-inflamed tongue. One day, however, in the midst of a bout of sore tongue, a growth was obtained by scraping, and this culture, together with three others, two of which were cases of tongue sprue in children, formed the basis for a preliminary note[2] entitled "A Monilia Found in Certain Cases of Sprue."

From that time to the present, I have made 240 cultures from the tongue, and 50 from the feces in 197 persons, all my own patients and all under my constant observation save five. I divided my sources of culture into three groups: (1) Cases of clinical sprue. (2) Cases with symptoms indicating involvement of the digestive tract, chiefly of a fermentative nature ("gastric and intestinal dyspepsia," etc.), or those presenting a simple stomatitis. The clinical picture of sprue lacked clearness in this group. In this group are included cases entirely cured of a past typical sprue. (3) Cases surely not sprue, and bereft of past or present history of disease of the digestive tract.

The first group consisted of 49 cases; 27 presented a clear picture with the four cardinal symptoms of complete sprue at the time of examination, and an actively inflamed and typical sprue tongue; 20 were cases of the intestinal type at the time cultures were made, but 7 gave histories of having had the complete picture previously;

[2] Jour. Amer. Med. Assoc., 1915, lxiv, 810.

2 were cases of tongue sprue, but also gave previous histories of the complete type.

All were promptly positive for monilia. Forty gave the cultural characteristics of the new monilia only and the remaining 9, apparently identical on Sabouraud's glucose agar, have not yet been grown in the required media. This gives a percentage of 100 for this group positive for monilia, all probably identical with the new species.

The second group consists of 82 cases. There are many in which no justification for a suspicion of sprue exists, but they are retained in this group because they give past or present histories of gastro-intestinal disturbance. They may be subdivided as follows: (1) Cases whose histories are suggestive of sprue, and in whom some symptoms still exist. These histories do not, however, justify a positive diagnosis. There are 19 in this subdivision. One gave a positive culture for the new species. Four gave monilias of type entirely distinct from mine, and in 3 of these cases the diagnosis of pellagra was pending. In one of these it has been positively confirmed. Five are frank cases of pellagra now, and all were negative for monilia after repeated search. (2) Cases with a history of gastro-intestinal vagaries in which the dominant note is usually "fermentative dyspepsia." There are 29 in this subdivision: 14 were positive for monilia, 7 for my species and 7 clearly not mine. (3) Cases with inflamed tongue alone. There are three such cases, all negative for monilia. (4) Cases giving a clear history of past sprue generally some years back. There were 20 of these, and all were negative for monilia. (5) Five cases with a colorless history, or a history not diagnostic of sprue, which I failed to see as cultures were made and sent in by colleagues. All were negative for monilia. (6) Six cases with good histories of sprue awaiting confirmation by cultures. The preliminary plate cultures were mature at the time of my leaving San Juan. All seem to be of the type to which the new species belongs.

Twenty-five, therefore, of the 82 cases in this group yielded monilia on culture, but only 14 belonged to the new species, a percentage of 17 for the new species.

The third group consists of 66 cases. No one of these presented

any symptoms of sprue, and many were apparently healthy in all respects. Four yielded monilia; two positive for the new species, the other two being entirely at variance therewith. The rest were negative for monilia, giving a percentage of three in this group for the new species. Animal experimentation will be detailed when completed.

The laboratory study of sprue has been limited to the working out of cultures, and this, naturally, has consumed much time, especially when one considers that all of the steps from the making of media, to titration, from collection of pathologic specimens, to their cutting, mounting and staining, has with negligible exceptions, been done personally by the writer. Nevertheless, a few remarks may be made on this subject.

Small laboratory animals are susceptible to inoculation by the new species usually dying of a general mycosis in a few days if the monilia has not had its virulence weakened by age, or too frequent transplanting. A large Belgian hare received a few drops of a ten-day culture of the monilia, recovered from the patient mentioned in the forepart of this paper, by hypodermic injection into the muscles of the tongue. Death occurred from general mycosis in seventy-five hours, and the necropsy cultures were made from liver, spleen, kidney, lung, heart's blood, and the muscles of the tongue. These cultures resulted directly pure for the new species in twenty-four hours. An interesting side-light is thrown by the morbid anatomy of this hare upon the statement of most writers who have had the good fortune to autopsy cases of sprue to the effect that the mucous membrane of the bowel is heavily coated with a white, grumous layer. Owing to the leaking of the syringe, the animal had received by the mouth from 1 to 2 grams of the culture, and upon examining the stomach and small bowel, they were found heavily lined with a white, creamy coating, examination of which demonstrated the immense preponderance of yeasts. To this it should be added that this animal, distinct from rats and guinea-pigs intraperioneally injected, had a sharp diarrhea and an enormous production of gas before death.

Intraperitoneally, two white rats were injected, one with a glucose bouillon culture of the new species recovered from another American,

who like the first died of the disease; the other with a similar culture from the daughter of a physician dangerously ill of sprue in the stage of marasmic toxemia. Both animals died of general mycosis, and from both, pure cultures were directly recovered from all the principal organs.

A hare who had proved himself resistant to the intraperitoneal injection of an old culture of the monilia which promptly killed the first animal, received in the tissues of the ear 4 grams of a bouillon culture and three weeks later it was found that the entire organ was the seat of a "blastomycotic" ulcer.

Feeding experiments, however, have been disappointing, although not yet persistently and systematically worked out. A guinea-pig of about 1000 grams was fed the new species in pure culture mixed with malted milk, it having been previously fed throughout a period of ten days with malted milk alone. Diarrhea and gaseous distention were produced and after three weeks the animal died. The histopathologic picture has not been worked out, but cultures from the organs were negative, save from mouth and stomach, which were positive for the new species and from the spleen which gave a culture apparently unlike the new species.

A monkey similarly fed, became weak, morose and emaciated, with sharp diarrhea, and the predominating organism in his stools is a yeast which in culture proved to be the new species of monilia.

In all feeding experiments, one should bear in mind that we are dealing with an organism of confessedly low virulence, and much patient and careful work must be done to elicit results worth citing as confirmatory.

The original technic of Wassermann was applied to the complement fixation test for cases of sprue by Gonzalez Martinez of our Institute of Tropical Medicine just as I was leaving the Island for the United States to attend this meeting. I selected three strains of the new species from among my cases and an antigen was prepared from these. Twelve cases not sprue were negative, and 4 clinically and bacteriologically sprue were positive. It is interesting to add that since that time all cases not sprue, and awaiting the Wassermann reaction for syphilis are subjected to the complement fixation test for sprue and are so far all negative.

Monilia Species Undetermined. The organism is a typical monilia reproducing by side-buds and terminal conidia from specialized hyphæ, as well as by budding from yeast forms. Ascospores are never seen, but chlamydospore-like bodies are frequent, especially in older cultures. The yeast is round, from 2 to 7 microns in diameter, averaging from 3 to 4, with clear, clean-cut outline, usually containing a relatively large refractile eccentric body, and a much larger, faintly outlined vacuole. Tendency to mycelial formation is seen by the round yeasts enlarging and becoming oval. As the yeasts become larger, many active, highly refractive bodies of the size of a staphylococcus race incessantly about within the organism reaching their largest number and greatest size in the chlamydospore-like, thick-shelled forms and frequently passing out into the fluid medium in which they grow, thus confusing the novice into believing that a contaminating coccus may complicate his apparently pure culture.

The mycelium is well developed, usually very abundant and presenting sparsely branching hyphæ, sometimes over a thousand microns long which consist of articles from 10 to 60 microns long by 1.5 microns broad, the usual length being 15 microns. These hyphæ are of two distinct varieties; thin, often granular and 1 to 1.5 microns wide, and thick, often clear and 2.25 to 3 or 4 microns wide. The latter variety, at times without apparent structure interiorly, is more frequently punctuated at regular intervals by the highly refractile bodies described as nuclei in the round and oval yeasts. These are from $\frac{1}{2}$ to 2 microns in diameter and give a brilliant beaded appearance to the article. They stain as for chromatin by Giemsa. At times with the refractile bodies, at times without them, articles are seen frequently to have rectangular vacuoles of the same refractive index as though seen in the larger yeasts, thus dividing the article as it were into compartments and giving the hyphæ the appearance of a bamboo pole sawn longitudinally. In old culture many large yeasts are seen of 10 to 13 microns diameter as also involutive forms of bizarre and clumsy outline, empty, collapsed chlamydospore-like bodies and heavy shelled prickle cells faintly suggesting the ova of ascaris lumbricoides.

Staining Reactions. The best class of stains for this organism belong to the Romanowsky series. I personally prefer staining overnight in a weak Giemsa as by it the nuclear elements come out beautifully. The only satisfactory stain I have yet found for the outer shell of the mycelial threads is by Bodin's Victoria blue method. For staining in tissues there are only two methods that can be recommended and they are both of the highest excellence. The first is Weigert's fibrin method giving fine contrast by Gram's application. The second is Bodin's Victoria blue method. This may be summarized as follows: (1) Paraffin sections of mercuric chloride, absolute alcohol or formal fixed tissue sections not over 5 microns; (2) after usual preparation for staining immerse for five minutes in a 1 per cent. erythrosin, aqueous solution. Wash well; (3) twenty-four hours in equal parts of a saturated alcoholic solution of Victoria blue and distilled water; (4) thorough washing in water and Weigert's stronger Gram solution for five minutes; (5) thorough drying and differentiation in aniline oil and xylol, equal parts; (6) thorough washing and clearing in xylol; (7) mount in balsam.

Cultural Peculiarities. The first labor was that of finding a specific medium. That one has been found in Sabouraud's glucose agar, 4 per cent. + 2, is evident to anyone who cares to try it. As far as these yeasts are concerned it is ideal, as bacterial growth is efficiently inhibited even in strokes from feces and agar plates, the monilia standing out with unfailing precision as moist, white colonies of sharply contoured lines.

In culture from the tongue, a section lifter is sterilized in the flame and the borders and tip are gently scraped, the grumous material being spread upon a Sabouraud glucose agar slant by means of a sterile platinum loop. Twenty-four to forty-eight hours is all that is usually needed to bring out a monilia which is plated by the familiar three-plate method, and is easily recovered in another twenty-four to forty-eight hours in pure culture. For feces the Sabouraud agar is poured into a Petri dish, allowed to cool and harden, and is infected by parallel strokes. Suspicious colonies are then plated by the three-plate method. These methods were strictly observed in all cultures except that two, instead of three plates were frequently used.

The following media were employed in studying the species under consideration: Plain agar, glucose-, maltose-, levulose-, saccharose-, galactose-, lactose-, manite-, dextrin-, erythrite-, raffinose-, dulcite-, isodulcite-, inulin-, and nutrose-agars. Loeffler's blood-serum mixture and plain blood serum; potato, plain and glycerinized; carrot, plain and glycerinized; plain gelatin, 20 per cent. + 1; plain and litmus milk; beer wort; Dunham's peptone solution; ox bile; plain bouillon, sugar-free bouillon; glucose-, maltose-, levulose-, saccharose-, lactose-, and mannite-, bouillons at 2 per cent. + 1 and galactose-, dulcite-, dextrin-, raffinose-, arabinoso-, inulin-, erythrite-, amygdalin-, asparagin and isodulcite at 1 per cent. + 1.

The first four strains and several others later in the series were sown in all of these media and carefully checked upon as follows:

All cultures were run for at least two weeks and daily notes taken of each before deductions were made. Before final conclusions were reached the purity of the culture was tested. Solid media were allowed to run several months, especially gelatin cultures. All media were carefully titrated, as a rule to + 1 by the rules of standardization of media recommended by the Bacteriological Committee of the American Public Health Association. Incubation was practiced at 33° to 35° without rubber tops to the tubes, these conditions being apparently most favorable to the growth of this monilia.

For fermentation tests, each culture in any sugar medium consisted of a fermentation tube, its control tube for final titration, and a litmus tube and its control to demonstrate daily progress in changing reactions. Incidentally it may be remarked that without titration by some such standardizing method as the one named above before sowing and at the close of the fermentation test, conclusions are greatly invalidated, as important and delicate reactions are quite missed. All sugar media were sterilized at the temperature of flowing steam for from ten to fifteen minutes on each of three successive days. Autoclaving splits the sugars. At the close of the period required for a complete fermentation test, the uninoculated media, which has been incubated along with the rest, was first titrated; then the inoculated media. Titration was

performed in each case both hot and cold and the results recorded. The varying daily gas production was recorded as was the daily reaction in the corresponding litmus bouillon.

The monilia in question was found to prefer an acid, although it will grow well in alkaline media. Its adaptability is further shown in that on every medium tried it grew without difficulty, but it flourishes most luxuriantly on glucose, levulose, maltose, saccharose, galactose, and carrot.

The characteristics of the organism are best elicited by Sabouraud's glucose agar, carrot, blood serum, plain gelatin, litmus, milk, and by fermentation tests in glucose, levulose, maltose, and saccharose bouillon (2 per cent. + 1) and galatose bouillon 1 per cent. + 1.

On Sabouraud's agar in from twenty-four to forty-eight hours a clean-cut, round, hemispherical, smooth, creamy white, moist, refractive colony is produced of the consistence of thick cream. Small colonies are very beautiful under the lower power seeming to be like silvered mosaic. Later they tend to become acuminated in the centre and rapidly run together to form a thick cream all over the agar. They give off a yeasty smell and remind me of some Porto Rican bread and the stools of my cases. A young culture on solid media is not given to the production of mycelium but in the water of condensation it is abundant. Later the smooth creamy layer in some media, often apparently due to a mere bagatelle of half a per cent's difference in acidity of the original media, becomes knarled and twisted like a bunch of worms or the roots of a vine—or even like a delicate honeycomb.

The growth on carrot is distinguished by its tendency to rise high and stick rather closely to the line of plant, giving the appearance of heavy bits of raised embroidery. On blood serum a fine, not raised, at times almost invisible layer is made out. No liquefaction nor decolorization takes place. The growth in gelatin is remarkably faithful to type. It does not liquefy the media, stabs showing a limited round growth on the surface and fine hair-like lateral shoots all the way down to the lower extremities giving the appearance of a test-tube cleaning brush.

Milk is not coagulated and litmus milk grows steadily more and more alkaline. There is no period of acidity nor decolorization.

In discussing the sugar tests I shall have to take issue with the eminent authors whose versatility has enabled us to make use of these valuable but much over-rated means of differential species Whether these gentlemen used our exact American methods of titration is open to speculation. They do not say that they did but I suspect that they did not. Had they done so perhaps Castellani and Chalmers would not offer such a bewildering series of "species" of monilia to the interested reader.

Such "species" as are to be depended upon not to produce gas when they are supposed to produce acid alone in a certain sugar bouillon, especially when they furiously ferment glucose, maltose and levulose, do not seem to me good. For one thing stands out quite clearly in these sugar tests: If a monilia produces acid, it is likely to produce gas, sooner or later. I have sown strain IV on one occasion and produced acid and gas in glucose, maltose and levulose; acid alone in saccharose and galactose. Two weeks later I have sown the same monilia, not from the culture on sugar media, possibly by that time educated to ferment sugars, but from the original source of the first culture. The result of this re-sowing was gas and acid in saccharose and galactose, as well as in the first three.

The species must not therefore be lightly made on sugar tests alone, when solid media, morphology and hanging drop specimens not to mention inoculation results in animals, complement fixation tests, etc., speak for unity. In general, however, sugar tests are a wonderful help if one will only remember that a lively acid and gas produces in glucose, levulose and maltose will often do likewise in saccharose and galactose.

The species I have before you tends toward alkalinity in all other sugar-media, with the possible exception of mannite and dextrine apt to remain unchanged as well as in plain and sugar-free bouillon. The characteristics of this monilia in bouillon is to leave the media clear, even after very long growth, with a more or less abundant sediment at the bottom of the tube. The growth at the

surface varies, being almost nil if the organism does not grow vigorously in the particular media, very heavy if it does. Heavy growths at the surface produce a pellicle with a thick collar at the circumference which in the process of evaporation of the liquid is drawn out into a belt around the inside of the tube. Later this pellicle falls to the bottom and a new one takes its place. The superficial growth is more apt to have a predominance of mycelium, the sediment an excess of yeasts.

Conclusions. Bahr's evidence in favor of regarding sprue as a "blastomycotic" infection is as follows:

1. Yeast cells and mycelial elements are found intracellulary in scrapings of the tongue lesions at an early stage of the disease, but cannot be found at a later stage in scrapings of the same structure when inflammatory symptoms have subsided.

2. Yeasts are the only organisms found in the deep layers of the tongue in microscopical sections; the evidence that this infection is not one of recent date receives support from the chronic inflammatory changes in the corium of the papillæ and from the presence of Russell's bodies in this situation.

3. The desquamation of the epithelial cells, accompanied by subacute inflammation of the tongue and of the esophagus, are changes such as would be expected from a study of the mode of growth of the thrush fungus and of its low order of virulence.

4. A general infection of the intestinal mucus with yeasts was found in sprue post-mortems, but no such a general infection in 26 cases of other chronic wasting diarrheas.

5. The stools of sprue, their frothy and gaseous character, are such as one would expect in a blastomycotic infection of the intestinal canal.

6. The relapsing nature, the chronicity and latency of the disease, are compatible with what is known of the life history of the blastomyces, their periods of attenuated growth and powers of sudden recrudescence.

7. There is no evidence in favor of regarding the sprue yeast fungus as being otherwise than identical with the thrush fungus (Monilia albicans), an organism possessing a very low pathogenic power, but it is possible that under certain conditions, as for instance

in the tropics, this power may be greatly augmented. In support of this view I may add that it is a well-recognized fact that there are numerous varieties of yeasts employed in brewing beer and in making wine, and the predominance of one variety in certain districts imparts to the local wine its characteristic flavor, which, though differing widely from each other in their powers of growth and fermentation, yet resemble each other minutely in their morphological and cultural character. May it not be that their pathogenic as well as their other properties are capable of being influenced by local conditions?

8. Wasting and anemia, both symptoms of sprue, can be produced by continuous intravenous injections of small doses of broth cultures of a pathogenic yeast; moreover, a degeneration of the hepatic capillary endothelium, apparently similar to that found in the sprue spleen, may be produced in these animals by the same means.

9. Diarrhea, atrophy of the lingual papillæ as in sprue, digestive disturbance, and an aphthous ulceration of the mouth are commonly found in infants the subjects of thrush infections in temperate zones.

10. It is possible that obscure diseases of the alimentary canal in children in temperate zones, such as Gee's celiac diarrhea, are of the same nature as sprue in adults in the tropics. A hypothesis of this sort would explain the occurrence of sporadic cases of sprue in temperate zones.

11. The local affection of different portions of the digestive tract with this fungus would best explain the varying clinical manifestations of sprue.

12. To maintain such a hypothesis it is necessary to stipulate for a third factor, a predisposing cause, which may exist in the local tropical climatic conditions, which favor a more precocious and luxuriant growth of all fungi, a matter of common observation to all laboratory workers in the tropics.

I am able to fully corroborate Bahr's evidence in all save human necropsy findings, as yet denied me, and with the exception of his statement that the sprue yeast fungus bears no evidence of being otherwise than identical with Monilia albicans. In this matter we

are not in accord as far as it may apply to Porto Rico where I have described a species, not *Monilia albicans*, present in 100 per cent. of my cases of clinically positive sprue. In addition to this I have isolated this new species from the centre of a loaf of bread from an endemic focus in Porto Rico.

I therefore offer the following tentative conclusions drawn from the work as studied in Porto Rico and described in the body of this paper and from the accepted facts presented by authors regarding the human histo-pathology.

Conclusions. (*a*) *Clinical*:

1. Sprue is usually a mild disease with a veiled picture in which intestinal fermentation is usually present, a tendency to spontaneous cure and a ready submissiveness to a non-carbohydrate diet.

2. Tongue lesions are often clinically and histo-pathologically indistinguishable from ordinary thrush, a disease due as a rule to monilia albicans.

3. Clinically and histo-pathologically the picture of the tongue is projected on through stomach to intestine.

4. Chronic intoxication supervenes after well-developed sprue, and the liver atrophies without cirrhotic changes, secondary anemia making its appearance.

5. The intestinal lesions produce large, acid, frothy, white stools with excessive gas production, and full of yeasts. The character of these stools does not warrant the belief that serious ulceration change take place.

6. There is a tendency to chronicity and to periods of latency in which decided betterment or apparent cure may take place.

7. Drugs are of little avail save when used symptomatically for definite clinical crises and no specific has yet been found.

(*b*) *Epidemiological:*

1. Sprue is a disease of towns and cities where bread is a staple food.

2. Sprue is apparently rare in the country districts where bread is not at least a daily food and where often it is eaten only at long intervals.

3. Family endemics are noticeable.

4. There seems to be a racial predisposition to sprue in persons of northern birth.

(*c*) *Biological:*

1. A monilia, not heretofore described, and of undetermined species is apparently constantly found in cultures from the inflamed tongue or feces of persons suffering from sprue in Porto Rico.

2. This monilia has been found in the centre of a cooked loaf of bread baked in an endemic zone.

3. This monilia has been found in certain cases of fermentative disturbance of the intestine in which the complete picture of sprue is not developed.

4. The monilia is found in only 3 per cent. of persons, apparently entirely healthy or, at least, free from any gastro-intestinal disturbance.

5. The complement fixation test is positive for all of the reduced number of cases of complete sprue in which it has thus far been applied and negative for several times that number of persons without sprue.

6. This monilia is not only productive of mycotic septicemia in small laboratory animals injected with virulent culture but will produce severe and intractable mycotic ulcers in their tissues when they are relatively immunized to the extent of preventing a mycotic septicemia.

THE OCCURRENCE OF SPRUE IN THE UNITED STATES

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Tropical sprue, or psilosis, was probably first referred to in American literature in the writings of Dr. John Brickell,[1] a Dublin physician, who was an emissary of the Crown to the Cherokee Indians early in the eighteenth century. In his report he discusses the diseases of the colony of North Carolina, and in addition to yaws he mentions "white flux," which, in all probability, was the disease described in 1776 by Hillary, in Barbadoes, as sprue. The identity of this West Indian sprue was never questioned by Sir Patrick Manson,[2] though Carnegie Brown[3] still contends that true sprue is limited in its distribution to tropical and subtropical eastern Asia. Fortunately for us many of our medical men, especially of the Army Medical Corps, became familiar with true sprue in the Philippines, and not only brought back with them this intimate acquaintance, but were able to identify the disease known as sprue in Porto Rico as true sprue of the East. In recent years many observers have suspected that sprue existed in the United States, but only in the last decade has anyone had the temerity to actually make the diagnosis except in cases invalided from the tropics. The return of missionaries from China and Ceylon suffering from sprue has given us many opportunities to become familiar with true Eastern sprue and to compare it with the milder type of sprue in the Southern States.

In 1905 St. J. B. Graham,[4] of Savannah, reported four cases of

[1] The Natural History of North Carolina, Dublin, 1737. Reprinted by the State Library of North Carolina.
[2] Tropical Diseases.
[3] Sprue, William Wood & Co., New York, 1908.
[4] Georgia Practitioner, August 15, 1905, xi.

sprue which had originated in Georgia. This observation was based on experience in the Philippines, and the correctness of the diagnosis can hardly be questioned.

In 1907 H. F. Harris,[1] of Atlanta, reported a number of cases of sprue. Later in that same year Searcy, of Alabama, reported the existence of pellagra, and Harris concluded that he had confused the two diseases; but a perusal of his careful report will convince anyone that at least some of his cases were sprue, and it is not improbable that his cases of pellagra were complicated by sprue. In a recent personal communication, Dr. Harris says there exist in Georgia cases which exactly correspond to tropical sprue of the East.

In 1909 R. Hessler,[2] of Logansport, Indiana, published an article on sprue, but his experience seems to have been limited to cases invalided from the tropics. In 1911 J. K. Simon,[3] of New Orleans, reported a probable case of sprue.

In 1912 I called[4] attention to the existence of sprue in the United States in connection with the recognition of pellagra. The two diseases are greatly confused, for reasons to be mentioned later.

At the last session of the American Medical Association, Hiatt and Allan[5] reported a number of cases of true sprue. Some of the cases were invalided from Porto Rico, but in one instance, at least, the case originated in North Carolina and the victim had never been out of the state. The most valuable feature of this article is the comparison of the disease brought in from the tropics and the disease as it occurs in this country. These observers have had the opportunity to study the disease from the two sources, and their conclusions are most important in settling this disputed point.

At the School of Tropical Medicine of Tulane University no case has yet been observed which originated in the United States, though quite a number from the West Indies have been studied. Notably among the latter is an unpublished case of Dr. Allan Eustis, with an autopsy by Dr. C. W. Duval. The case came from the Charity Hospital in New Orleans.

[1] Tropical Sprue, Report of the Georgia State Board of Health, 1907.
[2] Jour. Indiana State Med. Assn., April, 1909. [3] South. Med. Jour., July, 1911.
[4] A Treatise on Pellagra, 1912, Appleton & Co., New York.
[5] Jour. Amer. Med. Assn., 1914, lxiii.

The place occupied by tropical sprue in medicine at this time is most unsettled. Manson, Cantile, Begg, P. H. Bahr, and many others, especially of the English observers, count it a definite disease entity, while W. E. Musgrave and T. W. Jackson consider it a condition or state which may occur in conjunction with or as a complication of many of the diarrheal diseases of warm climates. This latter position is chiefly justified by the great variability in the descriptions of the various writers. Any condition attended with stomatitis and diarrhea has at one time or another been diagnosed sprue. Such a state of things is most unfortunate, and will probably not be corrected until the causative agent of sprue is definitely determined. Faulty use of synonyms has added greatly to the unsettled place of sprue in medicine. This is well illustrated in the use of hill diarrhea as a synonym when a number of observers are quite emphatic that this disease and sprue are not related in any sense. Manson gives in his list of the synonyms of sprue, Cochin-China diarrhea, while Dr. C. W. Stiles, in a personal communication, says that medical zoölogists understand by this term an infection with the Strongyloides stercoralis. This infection was found by Dr. Stiles in a number of the Southern States, with a distribution almost identical with that of uncinariasis.

Leonard Rogers,[1] in discussing the results obtained by him in the treatment of sprue in Calcutta with emetin and a streptococcal vaccine, remarks that the vaccine effect was quite striking, and in explaining it adds, "We should bear in mind that sprue is a purely clinical term, and there may be more than one causative agent, just as in the case of dysentery."

The term sprue has been adopted in the nomenclature of diseases of the Royal College of Physicians. The word was borrowed by Manson from the Dutch word "spruw," which was used in Java to designate the disease. If the original description of Manson is followed closely there need hardly arise confusion from the use of the term. Unfortunately the word has been so loosely used that it has tended to justify the position of those who contend that there is no such disease.

[1] Two Cases of Sprue Treated by Mouth Streptococcal Vaccines and Emetin Hydrochloride Hypodermically, Lancet, June 6, 1914.

W. E. Musgrave[1] proves one of the most convincing advocates of the view that sprue is merely a condition or state which may occur in various intestinal infections. In spite of this in one of his cases no parasitic cause was found, and the case must be regarded as sprue.

Mayo Robson[2] found that in many cases in which the diagnosis of sprue had been made, the condition was really a pancreatic disturbance of an inflammatory type, and that in other cases pancreatic involvement formed an important complication. In this connection it is interesting to note that Musgrave in one case noted that the pancreas was small and presented a dark, muddy appearance, but without areas of hemorrhage or necrosis. In another of his cases the pancreas was pale and firm. In Eustis's case the autopsy notes by Duval mention a resistance on cutting indicative of interstital changes of the pancreas. It seems probable that some cases of chronic pancreatitis have been confused with sprue or that in sprue the pancreas plays an important role. It is obvious that much study is needed to clear up the question of the possible relationship of the pancreas to sprue, and that this work must be along the lines of histological study of the pancreas and of pancreatic functional tests.

According to the original description of sprue by Manson there is a definite symptomatology which should save much of the present unnecessary confusion. It is a chronic disease occurring in the tropics and in certain subtropical sections which is characterized chiefly by a peculiar type of diarrhea, by stomatitis, by decrease in the size of the liver, and by marked secondary anemia. There is a tendency to frequent recurrences and the downward course. The diarrhea occurs chiefly in the morning hours, and is unattended by tenesmus, blood, or mucus. The movements are semiliquid, though at times more nearly liquid, acid in reaction, and contain much gas. The odor is regarded as peculiarly foul. The color is light, due to a colorless reduction product of hydrobilirubin known as leukobilirubin. In addition to this the large amount of fat in the stool contributes to the light color. The size of the stool is a

[1] Sprue, or Psilosis, in Manila. Amer. Med., March 8, 1902.
[2] British Med. Jour., July 27, 1907.

notable point, one which was emphasized by the late J. H. Musser as a valuable sign in pancreatic disease. In addition to the failure in the absorption of fats it is generally claimed there is a defective carbohydrate digestion. P. H. Bahr[1] found in his Ceylon cases that the fat absorption varied from 70 to 90 per cent., and that there was a complete absence of all pancreatic ferments. In a case of sprue from Porto Rico, Pratt and Spooner[2] found in addition to the intestinal disturbance pancreatic insufficiency which was indicated by the Einhorn-Schmidt thymus test and the Sahli glutoid capsule. The absorption test showed a fat loss of 45 per cent. and a nitrogen loss of 15 per cent. Though the stools were light in color there was a definite reaction for hydrobilirubin by the Schmidt test. The stools were yellow and voluminous, and contained many oil droplets as well as crystals and flakes of fat. It will be noted that these observers found a much greater fat loss than did Bahr. In a recent personal communication, Dr. Pratt mentions a case of sprue without pancreatic insufficiency in which the fat loss was found to be 59 per cent. He thinks that in this case the intestinal lesion is probably responsible for the condition.

The reduction in the size of the liver is not distinctive of sprue, as it occurs in other like conditions, as, for example, pellagra. It is the result of the general condition of malnutrition. Likewise, the anemia and marked prostration are of no particular significance from the diagnostic standpoint.

Sir Lauder Brunton[3] makes small mention of the shrinkage of the liver or the type of diarrhea, but lays particular stress on the aphthous stomatitis. Unfortunately, there is as much diversity in the description of the mouth symptoms as of the character of the feces. The original account of Manson is the most accurate, and should be followed. He recognizes definite stages through which the inflammatory process passes. In the beginning there is simple hyperemia, which is followed by denudation of the epithelium, and this, in turn, is followed by the formation of minute herpetic vesicles which occur singly or in groups, and are surrounded by inflam-

[1] Soc. Trop. Med. and Hyg., London, 1914.
[2] Jour. Amer. Med. Assn., lix, No. 3.
[3] Edinburgh Med. Jour., 1900.

matory areolæ. The vesicles rupture, leaving small, superficial erosions which are very painful. Congestion and swelling of the fungiform papillæ, particularly about the tip and edges of the tongue as well as superficial cracks on the dorsum, are also mentioned. From this account of Manson the various writers have departed in varying degree. Most writers are content if there is glossitis or esophagitis to pass over the further consideration of the degree or kind of process and count it a positive symptom. Because of this lack of accuracy there is great confusion with a number of conditions, but chiefly with pellagra. It is to be recalled that in pellagra, as a rule, there does not occur definite ulceration, though Crombie's molar ulcer has been noted by H. F. Harris. There is no reference in sprue literature to salivation, which is so conspicuous a symptom in pellagra. The pain from glossitis, pharyngitis, and esophagitis is much more acute in pellagra than in sprue.

W. Allan[1] has called attention to the marked similarity of the symptoms of amebic dysentery and pellagra when the skin eruption of the latter is absent. This same warning should be mentioned in connection with the differentiation of amebic dysentery and sprue. This difficulty is made the greater by the fact that sprue may complicate amebic dysentery. In amebic dysentery the simple fact of the occurrence of stomatitis and diarrhea (the two symptoms so often counted sufficient for a diagnosis of sprue) will lead to error without a study of the feces.

The disease most frequently confused with sprue is pellagra, and it is this fact which justifies this report. There is so much similarity in a portion of the disease picture of sprue that some writers, notably J. Burnet,[2] of Edinburgh, and C. E. Stewart[3] argue that the two are in reality one and the same.

In the United States the diagnosis of pellagra in the absence of skin lesions is made with considerable possibility of error. It may be that in those countries where the disease has occurred for a much longer period, the medical profession has acquired more skill in its recognition, basing their opinions on signs other than the skin

[1] New York Med. Jour., December 18, 1909.
[2] Jour. Amer. Med. Assn. (Abs.), August 9, 1911.
[3] Tr. XVII Intern. Med. Cong., 1913, Sec. XXI, Trop. Med.

manifestations. For the present, at least, we are not justified in making such a diagnosis without skin lesions unless the history of a past outbreak is quite definite. In reviewing my cases, which began in 1905 and include several hundred, I find that at the time of examination the skin lesions were wanting in a large number, and a note is made leaving doubt as to the correctness of the diagnosis. In following up these cases it is interesting to note that a considerable proportion never developed the necessary symptom for such a diagnosis. A number have died of other diseases and only a comparatively small portion were cases of pellagra. A large part of these cases we now know suffered from tropical sprue, which was supposed not to occur in this country. Emphasis should be placed on the fact that in spite of an experience of several hundred cases of pellagra, extending over a period of ten years, any diagnosis made in the absence of skin lesions at that time was simply guesswork.

In an editorial in the *London Journal of Tropical Medicine and Hygiene*[1] the question of the probability of the identity of sprue and pellagra is strongly argued. The writer finds a marked similarity in the stools in both diseases as well as indicanuria and pathological changes in the intestinal tract which closely resemble one another. Tuczek found in pellagra an attenuation of the intestinal wall as a result of atrophy of the muscular coat and also occasional hyperemia and ulceration of the large intestine. The editorial notes, further, that in sprue the mucosa is almost entirely destroyed and is replaced by a structureless substance containing leukocytes. The submucosa appears much thickened and fibrous tissue is abundant. The muscular coat is greatly thinned. The argument is concluded by the statement that the gastro-intestinal symptoms which are prominent in both conditions are strikingly alike, and that results obtained from examination of the gastric contents, stools, blood, and urine reveal almost identical conditions. The writer thinks that the nervous and mental symptoms which occur in some cases of pellagra have been given undue prominence. Singer,[2] working with the Thompson-McFadden Pellagra Commission,

[1] Jour. Trop. Med. Hyg., London, September 15, 1913.
[2] First Progress Report of the Thompson-McFadden Pellagra Commission.

found the incidence of pellagrous insanity to be 40 per cent., which is much lower than the incidence in my own cases in North Carolina. This observer regarded the nervous manifestations as toxic, subsiding with the disease activity. The definite cord degenerations, so well described by Tuczek[1] and so abundantly confirmed in this country in the few years in which such study has been possible, would throw the weight of evidence on the side of a disease to be ranked with syphilis, which it more closely resembles than any other. In one of our earlier cases there was definite degeneration of the columns of Goll and Burdach in the dorsal and lumbar cord. The patient was a negress, aged seventeen years, who was suffering the first outbreak. It is not reasonable to assume that reparation of this organic change would have occurred had she not succumbed. As a rule, organic nervous change does not occur until the victim of pellagra has suffered at least three outbreaks. When it does occur as a consequence of some toxic action it can be counted that the disease has reached the stage from which there is no recovery. While there is a toxic pellagrous psychosis unattended by any definite cerebral lesion, it is to be remembered that the spinal cord alone does not bear the brunt of the whole process. The growing tendency to make light of the nervous consequences of pellagra is to be deplored. Equally as much so as syphilis does pellagra attack the nervous system, and it might not be going too far to say, more so. It is probably in this one feature that we see the most distinctive difference between pellagra and sprue, for in the latter the nervous system does not suffer.

In the beginning of the process it is often difficult to distinguish pellagra from sprue. Harris noted that in some of his cases the feces were typical of the sprue type, though the eruption of pellagra was present. It must be remembered in this connection that sprue may complicate pellagra. As a rule, the diarrhea of the two diseases may be readily distinguished. In pellagra the feces are generally more fluid, darker in color, not limited to the early hours of the day, and attended with more or less tenesmus and mucus. In sprue the stool is much larger than normal, quite light in color, acid in reaction, containing much gas, and usually occurring in the early

[1] Klin. u. Anatom. Studien über die Pellagra, 1893.

hours of the day. The essential differences, however, are to be found in a chemical study of the feces. For this purpose we used the Schmidt test diet to determine the ratio between the fats and nitrogen intake and the output in the feces. In this work we were guided largely by the advice of Dr. J. H. Pratt.[1] We feel justified in the assertion that in pellagra the fat loss and the nitrogen loss in the feces are not abnormal. In one case of great gravity, which resulted in the death of the patient a few days after the observation, we found that the fat loss was 5 per cent. and the nitrogen loss 7 per cent. In another case of long standing the fat loss reached 17 per cent. and the nitrogen loss was 6.63 per cent. In sprue the findings are quite different. It will be recalled that Sir Lauder Brunton, Begg, Mayo Robson, and others found evidences of pancreatic inactivity or actual disease in spure. J. H. Pratt has called attention to the danger of error in counting a pancreas which is found on examination to be increased in hardness as a diseased organ. A number of these observers have noted the macroscopic findings of interstitial changes in the pancreas, but this alone should not constitute sufficient evidence of organic change. Oftentimes such an organ is capable of full function in spite of this apparent overgrowth of connective tissue. Begg thought that the failure of his yellowed santonin treatment in certain cases was due to complications, chief among which was pancreatitis. Cammidge found that in the urine and feces of fourteen cases pancreatitis occurred six times.

With all of this evidence pointing so strongly to a disturbance of the pancreas in sprue we carefully studied a number of cases of pellagra to determine this possible relationship. Our findings were entirely in accord with those of Myers and Fine[2] working with the Thompson-McFadden Pellagra Commission. They found that in pellagra there was practically normal utilization of the various foodstuffs. The fat utilization was good in all cases, though in three of their series of fifteen it was slightly below normal. At times we find the stools in pellagra to be acid. The Sahli glutoid capsule test in one case showed no return in the urine in five hours,

[1] Amer. Jour. Med. Sci., March, 1912.
[2] First Progress Report, Thompson-McFadden Pellagra Commission.

and in this case there was an excess of meat fibers, but we found this to be exceptional. As a rule, the salicyluric acid appears in the urine in the normal time, the meat fibers are absent. The Schmidt beef-nucleus test, using the silk-gauze bags, was frequently tried, and in no case were there any nuclei to be found on sectioning and staining with eosin and hematoxylin. The test for trypsin showed its presence.

Observers in the tropics hitherto have been unable in many cases to distinguish between sprue and pellagra because of the absence of the skin lesions. The skin lesions of pellagra occupy only a small fractional part of the time of the outbreak, or may be so trivial as to be entirely overlooked. Such confusion may be avoided by a study of the feces. A fatty diarrhea alone would be the best single symptom for the diagnosis of sprue.

Summary. 1. Tropical sprue occurs in the Southern States, where it is frequently confused with pellagra.

2. Sprue is a definite disease entity with a definite symptomatology, which when followed should cause no difficulty in diagnosis.

3. There is much evidence tending to justify a further study in order to determine whether the characteristic sprue stool is or is not due to a lesion of the pancreas. The deficiency of pancreatic function in sprue may be due to actual pancreatic change, or a disturbed intestinal function may play a part in the findings.

4. The only certain means of differentiation between pellagra and sprue is a study of the feces. Fatty stools with great fat and nitrogen loss are characteristic of sprue, while in pellagra the fat and nitrogen absorption are about normal even in spite of the diarrhea.

5. Sprue may complicate any of the intestinal diseases and add to the confusion in diagnosis, therefore, for the present at least, the diagnosis of pellagra should not be made in the absence of skin lesions except when the history of a former outbreak is definite.

I am especially indebted to Professor Isadore Dyer, of Tulane University School of Medicine, and to the librarian of that school for many kindnesses. To Mr. George F. Catlett I am indebted for material help in definitely determining the chemical differences in the stools of pellagra and sprue.

DISCUSSION

Dr. Joseph H. Pratt: It is important for physicians in the North to study sprue, as the disease occurs there and is usually unrecognized. It may not develop for some time after an individual leaves a warm climate. It is a disease in which recovery depends largely on the proper dietetic treatment, hence the importance of a correct diagnosis early in the course of the disease.

I have seen four cases in Boston and all of them had been treated by clinicians who failed to recognize the disease. Every case of fatty diorrhea should be examined with the possibility of sprue in mind. The characteristic yeasty stools may not be seen when a patient is on a milk diet, but the stools will still be bulky and clay-colored. On microscopic and chemical examination much fat will be found.

Dr. Thomas Ordway: In certain stages sprue may be confused with pernicious anemia on account of atrophy of the tongue and the blood picture, which may show an anemia with a relative lymphocytosis.

THE VALUE OF SYMPTOMATIC TREATMENT

By JOSEPH L. MILLER, M.D.
CHICAGO

As compared with a few decades ago, drug therapy occupies a less prominent place in the treatment of disease, and inasmuch as most medication is symptomatic in character, it probably means that symptoms are less frequently treated than in former years. Is this to be considered a step in advance, or are we on account of our interest in scientific medicine negligent of an important detail in treatment? It is probably true that with the development of specific drug therapy and biologic products the physician has become more impatient with and less interested in treatment directed toward giving only temporary relief. Other important reasons, however, must be considered. The profession each year contains more and more men with careful scientific training. This training may have led them to scrutinize more closely all methods of treatment through carefully controlled observations. The advance of pathological, physiology, pharmacology, and experimental therapeutics has furnished them with certain knowledge, and especially a new method of applying it. As a result of all this there has developed, as it appears to the writer, a certain healthy scepticism in regard to drug therapeutics.

Certain points should be considered before undertaking any symptomatic treatment. A few that might be mentioned are: Should this particular symptom be corrected? Does it interfere or assist in bringing about improvement or recovery? Will its modification interfere with making a correct diagnosis or obscure observation upon the progress of the condition? Having determined that a certain symptom should be treated, it is necessary to determine, if possible, the underlying pathological physiology and then the

agent to correct it. Not merely the chemical agent, but the necessary dosage and frequency with which it should be repeated in order to bring about the desired effect. To attempt to lower blood-pressure, at least under certain conditions, may be poor therapeutics; as for instance when due to increased intracranial pressure, where the rise in blood-pressure is an effort to avoid cerebral anemia. It is not improbable that hypertension of renal origin is an effort to increase the efficiency of a pathological kidney. Drug antipyretics, on account of their depressing action, have been largely abandoned in the treatment of prolonged fever. The recent investigation of Rolly and Meltzer and Ludke and others raises the question whether any method of artificially lowering temperature is desirable, as according to their experiments, at least a certain degree of fever favors the development of immune bodies. Before undertaking symptomatic treatment it is wise therefore to consider the compensatory resources of the body and not confuse compensatory action with disease symptoms.

In the severe acute infection if we decided the centres in the medulla are not functioning properly, can we modify them by certain drugs? We are taught by our pharmacologists that strychnin quickens and deepens the respirations and stimulates the vasomotor centre, frequently causing slowing of the pulse and a rise in blood-pressure. Now if these same results were produced at the bedside upon these centres, rendered abnormal by toxins, we would have in strychnin a valuable symptomatic remedy. Whether under the conditions mentioned and in the usual doses strychnin stimulates these centres sufficiently to bring about any appreciable improvement, is exceedingly doubtful, as shown by the observations of Cabot, Newburgh, and others. We must, therefore, conclude that either our conception of the pathological physiology is incorrect, and the recent work of Newburgh indicates that in this particular illustration this may be the case, or our pharmacology is at fault. Symptomatic treatment, however, when applied to the correction of undesirable symptoms by agents that have been demonstrated to correct these disturbances is strictly scientific and in this respect is placed at once on the same level as specific therapy.

There is another group of conditions in which symptomatic treatment is not only strictly indicated but in which the agents are at hand to give relief. Morphin when administered to a pneumonia patient with acute pleurisy not only relieves the pain, but deepens the respiration, improves the oxygenation of the blood, promotes sleep, and thus becomes far-reaching in its results. In an acute attack of pulmonary edema, morphin is often of considerable value, in a measure due to its relieving the patient's fears and thus lowering the arterial blood-pressure, and so permitting a restoration of function of the left ventricle. Morphin in acute biliary or renal colic relieves pain, and at the same time relaxes muscular spasm, thus allowing the calculus to escape. Adrenalin, by relieving bronchial spasm, may abort an attack of bronchial asthma. Angina pectoris when due to spasm of the coronary artery may be relieved by the nitrites.

There is another group of conditions in which symptomatic treatment may give only transitory relief, but when combined with other agents may give prolonged relief. This form of symptomatic treatment can only be considered scientific when associated with these additional measures. As, for instance, digitalis, although claimed as a functional remedy is nevertheless given to relieve symptoms, as, for instance, dyspnea. Alkalies are of value in relieving gastric hyperacidity. The digitalis, however, should be combined with restriction of physical exertion and the alkalies with the proper dietary measures in order to give lasting results. Outside of these mentioned or others of the same rational character there is a large group of symptoms the present-day treatment of which cannot be considered rational therapy. It is in this field that the clinical therapeutist can render real service. Here a process of elimination is necessary in order to place therapeutics upon the same high plane as the other branches of medicine. In order to determine the value of symptomatic treatment it is essential that the observer be familiar with the course of untreated disease. Individual variations must always be taken into consideration. Many patients with pernicious anemia grow progressively worse, others have prolonged periods of spontaneous improvement, the latter offering a dangerous pitfall for the unwary therapeutist.

Perhaps in the teaching of clinical therapeutics it would be wise to instruct the student first in the course of untreated disease. If possible to follow a few cases carefully in the ward, tabulating symptoms, their intensity and duration. He would thus be impressed with the importance of carefully recording symptoms and be in a better position to determine the effect of therapeutic agents, and so avoid the error of acquiring experience in clinical therapeutics in a haphazard and time consuming manner. For the purpose of arriving at accurate information, too much stress cannot be laid upon the statistical method, of which Dr. Osler has always been a strong advocate. While the impressions of our therapeutic accomplishments may be more pleasant to consider, it is carefully collected and recorded information that is of lasting benefit to medicine. Our therapeutics can be placed upon the same accurate basis as pathology and symptomatology. Symptomatic treatment is most important not only from the standpoint of the patient, but also for the purpose of clearing up the field of clinical therapeutics and he who undertakes a careful study of symptomatic therapeutics will be rendering a lasting service to medicine.

DISCUSSION

Dr. S. Solis Cohen: In the brief time allotted for this discussion, one cannot hope to treat fully the many interesting questions raised by the reader, much less to submit additional material of value.

Clearly, however, it is impossible, and would be worse than ridiculous, to attempt to lay down any hard-and-fast rules for the great variety of conditions that arise in practice. That acute and chronic forms of disease, that infections and metabolic disorders, that affections, *i. e.*, tissue changes in progress, and the infirmities which are the result of past affections, differ widely in their indications, is obvious. So, too, the measures appropriate to relieve a given symptom occurring under one set of conditions, may be extremely inappropriate under other circumstances. Nothing can relieve us of the obligation to exercise individual judgment in therapeutics, to adapt our measures to the particular case and the special moment. Still certain general considerations may well be held in mind.

The object of the therapeutist is conceded to be threefold: the facilita-

tion of recovery, the prolongation of life, and the promotion of comfort. In the pursuance of these ends, it is not always easy to distinguish sharply between symptomatic and other forms of treatment. Thus, for example, it has been made pretty clear in today's discussions that even a measure apparently so radical as the removal of the thyroid gland in Graves' disorder may properly be termed symptomatic. It does not remove the primary etiological factor, but simply breaks a vicious circle at what may be the most accessible point. In some instances this may be the wisest procedure, in others it may be quite the reverse. But to undertake it under a false impression cannot be wise in any case.

On the other hand, the best means of relieving pain in acute articular rheumatism, for example, may be the administration of the salicylates, a measure which in the present state of knowledge is the nearest approach to specific treatment at command. So, too, as Meltzer has shown, the application of magnesium sulphate in certain cutaneous inflammations not only relieves the pain, but tends to control the essential morbid process; and the reinforcement of antitoxin or phenol by the magnesium salt in tetanus, if not specific, is at least entitled to rank as a special method peculiarly applicable in the pathological condition presented. It is much more than symptomatic in effect.

Again, that measure which best controls the symptomatic paroxysm in frank malarial fevers, or relieves the neuralgic pain of a masked malaria, is quinin, our typical specific. The treatment is at once causal and symptomatic.

Or take the use of digitalis to overcome the results of cardiac decompensation—for example, dyspnea or effusion. Since this relieves by correcting the faulty mechanism of circulation, it is sometimes described as causal treatment. It is not; for it does not remove the cause of the cardiac failure —but is it any the less efficacious if we recognize its true position as a symptomatic measure based on functional pathology?

In other words, whether we call our treatment radical or palliative, etiological or symptomatic, specific or general, we ought to have a clear idea of what we intend by it, so that we may be able not only to estimate rightly its efficacy and adequacy, but also to determine whether to rely upon some one measure only, or to supplement or modify it by others precedently, conjointly or subsequently. And here, if time permitted, I would like to say much about the association of remedies—but this must be omitted.

Restricting the term "symptomatic" to measures which are designed purely to overcome symptoms –with possible reference to their mechanism, but without reference to the fundamental etiology—the effect of such symptomatic treatment may be simply the temporary relief of distress—as by the administration of a hypnotic; or the prolongation of life by the removal or counteraction of certain immediate or remote dangers—as,

for example, when tracheotomy or intubation is performed in edema of the larynx; or to promote recovery by sustaining life or diminishing the tendency to death, during the evolution of some morbid process running a definite course—as by the administration of pituitrin to maintain blood-pressure in acute lobar pneumonia, or the use of cold water in typhoid fever to diminish nervous irritation, to abstract heat and to promote elimination.

Under the influence of surgeons, there was for a while a tendency to avoid the use of opium for the relief of pain. Whatever may be the necessity in surgical cases for avoiding obscuration of symptoms, yet in non-surgical cases, the diagnosis being sufficiently clear and there being no counter-indication in the state of the kidneys, the relief of pain frequently stands out as an urgent indication to be met only by opium, which is thus an important factor in conserving strength, and permitting recovery to take place. We have all seen cardiac cases in which death would have taken place but for the immediate use of morphine symptomatically. Such treatment must, of course, be followed by measures based upon etiology or upon functional pathology; but the point at present is the urgency and efficacy of the symptomatic measure. In asthma of whatever origin, control of the paroxysm by appropriate symptomatic measures is a prerequisite to more thorough-going treatment for the removal of the underlying causes of the disturbance; and incidentally I may refer to the great value of aspidospermine, also symptomatically in certain instances, after the immediate relief given by morphine associated with atropine or scopolamine and strychnine.

But symptomatic treatment is not to be used in haphazard fashion. It must incorporate and coördinate with the general plan of management. Even our friends the eclectics, whose use of the term "specific" means only that a certain remedy will—as they say, "specifically"—overcome a certain symptom irrespective of its cause or mechanism, pay great attention to the association of symptoms. Thus, whereas they would consider aconite "specificially indicated" in the presence of a rapid, small, and hard pulse and a dry, reddened tongue, or "inflamed mucous membranes," they would employ veratrum to slow the pulse when the artery is full and the beat strong, especially if there is a "deep red stripe down the centre of the tongue" and "relaxed mucous membranes." So, too, our homeopathic friends lay great stress upon the "totality of symptoms" rather than upon any isolated symptom. I am not now discussing the dogmas or reasoning whereby either electics or homeopathists arrive at their practice—although incidentally I am glad to acknowledge my debt to eclectic empiricism, especially in the use of certain native American plants. I merely wish to emphasize the principle that even in purely symptomatic treatment, all of the symptoms present must be taken into consideration, before deciding upon the measure to be employed to alleviate or overcome any one

of them. In other words, the problem is always complicated by the possible untoward result as regards one symptom, of a drug or other measure which another symptom suggests. The therapeutic diagnosis, based on etiological and pathological diagnosis, seeks a measure or measures that will affect beneficially all the symptoms.

We are reading nowadays in the papers much of strategy and of tactics. In therapeutic strategy, symptomatic treatment has small place; but in the tactics whereby that strategy is made effective, it has an important place, and it is our duty as teachers to lay much more stress upon such tactical measures than we do at present.

But as said in the beginning, time will not permit a full statement of all the principles involved, to say nothing of their explication and applications. We are indebted to Dr. Miller for bringing this important matter before us, and I should like nothing better than on some future occasion to have a whole afternoon devoted to it.

Dr. George Dock: Dr. Miller has traveled a long way since reading his paper here on expectorants. I can only agree with Dr. Solis Cohen, that this question is an exceedingly complicated one, and one should not think it proved that because drugs check symptoms they are always to be used. For example, Dr. Miller spoke of the exhibition of morphine for the relief of pleuritic pain in pneumonia as symptomatic treatment with scientific sanction; but this relief can be obtained by the application of the hot iron, by the use of an ice-bag, or by the employment of dry cups. Perhaps these measures may be better than the use of morphine which might upset the digestion or disturb the production of antibodies.

Dr. A. Jacobi: For sixty years I have been using symptomatics; I do not mean only the things approved as ultrascientific, I mean things from the drug store on the corner. I am convinced that I have done more good with a dose of morphine to relieve the pain of pleurisy and to give the patient a good night's rest than Dr. Dock can do with his cautery. Unless you use in practical medicine symptomatics, you are helpless. Harrison law or no Harrison law, I would not be without morphine ever ready. In the pleuritic pain of early pneumonia, to withhold the relief to be had from a dose of morphine and to withdraw the sleep and rest it will bring, is not only to commit a therapeutic mistake, it is to commit a therapeutic crime.

But what I want to say is that I am delighted to hear a paper that reminds me that there are physicians present. This society was founded thirty years ago in the interest of practical medicine, but it is no longer what it was and a paper like Dr. Miller's comes almost as a surprise. The Association is departing from its great purpose. It is a great mistake to deny admission to so many able clinicians; there is opportunity elsewhere for presenting the work of laboratory investigators.

PATHOGNOMONIC ALTERATIONS OF THE CEREBROSPINAL FLUID IN SYPHILIS OF THE NERVOUS SYSTEM

By JOSEPH COLLINS, M.D.
NEW YORK

The cerebrospinal fluid of healthy individuals has a fairly constant constitution. Although we do not know its origin or its functions, we know that it is subject to alteration of constitution in many diseases, and especially in diseases of the central nervous system. Much study has been made to determine the specificity of such alteration, that is, whether there occur pathognomonic alterations of the cerebrospinal fluid in any disease. It need not necessarily show abnormality in any disease. It is usually altered in disease of the central nervous system, caused by pathognomonic organism (Diplococcus intracellularis, tubercle bacillus, poliomyelitis organism, Treponema pallida, etc.). It is most constantly altered in syphilitic diseases of the central nervous system. In the majority of syphilitic nervous diseases, it is altered in a fairly characteristic way, and in some the alteration is so constant and unvarying as to be considered pathognomonic. When the syphilitic disease of the central nervous system is predominantly of the meninges and bloodvessels, that is, when the brunt of the lesion is borne by the connective-tissue structures, the change in the cerebrospinal fluid is subject to wide variation, depending upon the intensity of the infection, the rapidity and extent of the pathological process, and upon the individual (vital resistance).

Meningeal Syphilis, Cerebrospinal Syphilis. When the pathological process is confined largely to the meninges, the circumvascular spaces, and the bloodvessels, the most conspicuous alteration in the cerebrospinal fluid, in addition to the positive Wassermann reaction, is an increase of the cellular elements of the fluid and particularly an increase of the mononuclear cells. If this increase amounts to 100 or more the cubic millimeter and the

polynuclear variety of cells are above 10 per cent., it may be assumed with much confidence that the syphilitic process is predominantly meningeal, it matters not what the clinical display is. If the fluid with these characteristics does not reduce Fehling's solution and shows no excess of globulin the assumption is even more certain. Furthermore, it is very likely that such cases will yield promptly to appropriate treatment, inasmuch as the pathological alteration in the cerebrospinal fluid can be quickly brought, approximately, to a normal state. Of a large number of cases to bear out these statements I quote two:

Case I.—Female, aged thirty-eight years, married. There is no history of syphilitic infection; she has borne three children and four miscarriages. Complaint: breaking pains in arms and legs, headache, insomnia, nausea, occasional vomiting, indigestion, constipation. Duration of symptoms, eighteen months. Has been constantly under treatment for dyspepsia.

Physical Signs. Liveliness of the tendon-jerks; tremor of the outstretched fingers and of the lips.

Laboratory examination: Serum, Wassermann, +; cerebrospinal fluid, Wassermann, +; cells (180 polynuclears), 1480; globulin, +; Fehling's, +; 0.6 gm. salvarsan intravenously.

Two weeks later: Serum, Wassermann, +; cerebrospinal fluid, Wassermann, +; cells, 149; globulin, +; Fehling's, +. Then 0.5 gm. salvarsan and a week later two injections of neosalvarsan, both intravenously.

Two months after the first laboratory report: Serum, Wassermann, −; cerebrospinal fluid, Wassermann, −; globulin, −; cells, 5; Fehling's +.

Case II.—Male, aged twenty-six years; unmarried; became infected with syphilis one month before he consulted me for the relief of headache, spasm of the left side of the face and left upper extremity, lethargy, stuporousness, dysarthria, and anarthria. The evolution of these symptoms occurred in three months. Physical examination was negative, save for a slight paresis of the motor branch of the right fifth and of the seventh cranial nerves. Laboratory examinations:

	October 7, 1913.	October 20, 1913.	October 31, 1913.	December 9, 1913.	December 22, 1913.	March 17, 1914.	June 5, 1914.
Serum Wassermann	++	+	−	+	−	−	−
Cerebrospinal fluid, Wassermann	+	+	+	+	−	−	−
Cells (12 polymorphonuclears)	533	171	70	34	16	12	5
Globulin	+	+	−	+	−	−	−
Fehling's	+	+	+	+	+	+	+

He received nine intravenous injections of salvarsan within two months and was then given salicylate of mercury hypodermically.

The Serology of One Hundred and Seventeen Consecutive Cases of Cerebrospinal Syphilis. Examination of the blood serum of patients with that form of syphilis of the nervous system in which the brunt of the lesion is borne by the connective tissues of the central nervous system, shows that the Wassermann reaction in the blood serum is positive in 88 out of the 117 cases; the cerebrospinal fluid Wassermann in 33 cases; excess of globulin in 46 cases. The largest number of cases, *i. e.*, 46 of the 117, show a positive Wassermann in the serum and a negative cerebrospinal fluid with a normal cell count. In 23 of these cases no cells were found, in 16 not over ten cells, in 4 not over twenty cells, while 2 cases had a cell count between twenty and thirty cells. The next largest group of cases, namely twenty-three, is that in which the serology is positive throughout and in which there is either a moderate or usually a marked pleocytosis. Eleven of these 23 cases had a cell count of more than one hundred, while it ranged between ten and eighty cells in 12 cases; 2 of these cases showed the largest cell count obtained in any of the cases, namely, 1882 and 1630 respectively. In 18 of the total of 117 cases the serology was negative throughout. In 5 of these cases there were no cells: in 8 between ten and twenty cells, and in the remaining five the cell count ranged between thirty and one hundred and fifty. In 13 of the total number of cases the serum Wassermann and the globulin were positive, while the Wassermann in the cerebrospinal fluid was negative.

In this group of cases a moderate pleocytosis is the rule: 1 case had no cells, 3 not over ten, 2 not over twenty, 3 not over thirty, 2 between thirty and fifty, while 2 cases have over one hundred and two hundred cells respectively. In 7 cases positive globulin was the only positive serological finding; while in this group the cell count ranged between ten and fifty cells, there was 1 case which showed over two hundred cells. In 6 cases both the serum Wassermann and that of the cerebrospinal fluid was positive, while the globulin test was negative. Only 1 of these cases had more than ten cells. In 3 cases the serum Wassermann was negative, while that of the cerebrospinal fluid and the globulin was positive. One

of these cases had not more than ten and two not more than thirty cells. In 1 case only was the Wassermann of the cerebrospinal fluid the only positive feature of the serology. The cell count was not over fifty.

Tabes and General Paresis. The cerebrospinal fluid taken from individuals whose brain and spinal cord display the reactions to the Treponema pallida that are known as general paresis and tabes is characteristically altered in from 60 to 75 per cent. of them.

The typical serological picture of tabes is: Serum Wassermann, +; cerebrospinal fluid, Wassermann, +; cells, 20 to 100; globulin, −+ (usually −); Fehling's, +.

Increase of lymphocytes is the most constant alteration of the cerebrospinal fluid of individuals with tabes. In 200 consecutive cases, 154 had cellular abnormality of the fluid. In 30 instances the number of cells to the cubic millimeter of fluid was under five, and in 16 of these there were no cells. Of the 154 cases, there were 23 which had upward of 100 cells to the cubic millimeter. Such cases we are accustomed to designate hyperlymphocytic tabes, and we have learned that they are more amenable to treatment than the hypolymphocytic varieties. Polynuclear elements in the spinal fluid of this variety of tabes is the exception, not the rule. The highest count in any patient of the 200 consecutive cases was 592. There were 50 instances in which the count was about 60, and 122 instances in which it was about 25.

We have never observed a case of hyperlymphocytic tabes with 1000 cells to the cubic millimeter in the spinal fluid. The extreme limit of the pleocytosis observed is well within 400 cells per cubic millimeter. The presence of polynuclear elements in the spinal fluid of this variety of tabes is rather then exception than the rule. Whenever found this phenomena is to be considered of very favorable prognosis. It must be emphasized at this juncture that the irritation is responsible for the pleocytosis whereas the spirochete *per se* is responsible for the positive Wassermann reaction. The one may be removed without in the least influencing the latter; so that we may therapeutically succeed in doing away with most, if not all, of the pleocytosis, leaving behind a Wassermann reaction

which cannot be influenced under any circumstances. Such a case is the following in this communication.

A gentleman, aged forty-seven years, recalled when his recollection was refreshed, that when a youth he had preputial ulceration of some sort to which he gave no attention. Four months before consulting me he experienced a sensation of heaviness in the feet and legs and occasional shooting pains. His complaint when I saw him was: Weakness of the legs and some awkwardness in his walking; cushion sensation under the balls of the feet, numbness in the peroneal region; occasional imperious desire to urinate. His physical signs were typical of tabes: Serum, Wassermann, +; cerebrospinal fluid, Wassermann, +; cells, 98; globulin, −; Fehling's, +.

From October, 1910, he has received 18 injections of salvarsan, 24 injections of neosalvarsan, 5 injections of salvarsanized serum, and 46 injections of salicylate of mercury.

His serum Wassermann test once a month remained positive up to May 29, 1915, when it was found negative for the first time and cerebrospinal fluid was likewise entirely negative. His symptoms at this time practically disappeared and he was discharging the obligations of an exacting professional duty, that of a general practitioner of medicine. On August 7, 1915, the serum Wassermann was again +.

The cerebrospinal fluid taken from individuals who have tabes reduces Fehling's solution in nearly every instance. In 12 cases only out of 200 consecutive cases did it fail to do so.

The globulin of the cerebrospinal fluid increased is in nearly 50 per cent. of the cases. So far I have not been able to associate the increase of globulin with any definite clinical type of tabes.

Out of the 200 cases there were 7 similar instances, that is, in which it was impossible to make the serum negative despite the most protracted administration of antisyphilitics.

It is of the greatest importance to determine whether the patient has recently taken treatment that deters the Wassermann reaction. I have gone through the histories of my cases with much care to determine this. Forty-one of the 63 cases whose serum gave a negative reaction had received mercury or salvarsan before coming under my observation, 22 of them had not.

Of the 27 patients whose Wassermann reaction of the cerebrospinal fluid was negative, 17 had received antisyphilitic treatment.

A study of these 200 cases of tabes throws interesting light on the incidence of tabes. The accompanying table sets this forth:

Males	161	
Females	39	
		200
History of infection—hard chancre	108	
Soft chancre	13	
Gonorrhea	20	
	141	
Denied	59	
		200
Treatment at the time of infection	107	
No treatment	93	
		200
Treatment later	102	
No treatment later	98	
		200

In 70 consecutive patients afflicted with general paresis, the majority of them in the early stage of the disease, and 58 of which were males and 12 females, the Wassermann reaction of the serum was positive in 47 instances, negative in 17, and refused or not recorded in 6.

The Wassermann reaction of the cerebrospinal fluid was positive in 53 instances, negative in 7 instances, and refused or not recorded in 10 instances.

The cerebrospinal fluid showed an increase of the cellular elements beyond the normal in 52 instances, no increase in 9, and no record in 9. The highest cell count of any case was 270. There were 9 instances in which the pleocytosis was above 100 and 16 instances in which it was above 50. The average cell count was 58, though the majority of instances showed a pleocytosis of from 30 to 50.

The globulin of the cerebrospinal fluid was increased in 45 instances, not increased in 15, and no record in 10.

It goes without saying that the denial of syphilitic infection on the part of the patient who has general paresis has very little weight. In this series of cases it was admitted in 29 cases, denied in 25, and nothing known of such an occurrence in 13. The results of treatment may be summarized in a sentence; although the constitution of the cerebrospinal fluid is modified in many instances by the administration of salvarsan and mercury, it was never made normal.

The characteristic precipitation of colloidal gold occurred in 97 per cent. of the cases of paresis. It will be recalled that Szygmondi suggested the use of colloidal metals to determine the quality of protein substances, and Lange attempted to determine the nature of the protein substance in the cerebrospinal fluid by an elaborate series of experiments with colloidal gold. It is not, however, in the work of Lange apparent that he came to any definite conclusion concerning the nature of the protein in the spinal fluid. The precipitation that he obtained with the use of colloidal gold suggested to him that it would be of great value in detecting syphilis. In our hands, however, we were unable to corroborate that colloidal gold, used after the manner described by Lange, is to be depended upon as a detector of syphilis in general, but it is the most reliable and unvarying phenomenon of general paresis. In view of the fact that workers have found discrepancies in using the colloidal gold reaction, Dr. David W. Kaplan, director of the clinical laboratory of the Neurological Institute, reminds me that strict conformation to the following conditions shall be made.

1. All utensils coming in contact must be not only sterile but must be subjected to repeated washings with distilled water, double distilled water and ether. No rubber should come in contact with any glassware during the manipulation of the test, which includes the preparation of the distilled water.

2. All reagents should be of the purest quality preferably of Merck's highest purity.

3. Instead of using a 1 per cent. formaldehyde solution, a 0.75 per cent. solution was used. The flasks used for the making of the colloidal gold must be of Jena's best quality.

4. Any flask showing at the end of twenty-four hours a deposit of gold is henceforth rendered useless including the solution contained therein.

5. Any solution which does not permit of the reading of ordinary newspaper print through the thickness of the flask is to be considered worthless for the reaction, nor is the solution serviceable if it does not present an absolutely clear cherry-red tint. Any shimmer of a yellow or brown tint makes the solution useless.

Any discussion of the cerebrospinal fluid in syphilitic diseases

of the central nervous system must include some reference to the effect of antisyphilitic medication: salvarsan and mercury. That such effect is often very striking everyone who has had experience in examining the cerebrospinal fluid knows. The cases cited are excellent examples. The effect of such treatment is first most conspicuously manifest upon the pleocytosis; second, upon the globulin; and third, upon the Wassermann reaction.

In meningeal and meningovascular lesions the effect of antisyphilitic treatment stands in direct relationship to the effect which the treatment obviously has upon the pleocytosis. In other words, as the pleocytosis diminishes and approaches the normal the symptoms recede. Unfortunately, however, the symptoms do not always continue "to improve" or disappear when the pleocytosis has been overcome and the reactions of the cerebrospinal fluid have been brought to normal. Especially is this true of tabes.

The technic of the Wassermann reaction employed is as follows

Standardization of reagents on the day when tests are performed.

Four units of amboceptor used (antisheep).

Half a unit of antigen; alcoholic guinea-pig hearts used with and without cholesterin.

Eighteen-hour-old guinea-pig complement.

In all tests 0.5 c.c. of spinal fluid was used.

DISCUSSION

Dr. B. W. Sippy, Chicago, Ill.: Having brought the method to this country from Lange's Clinic, and having reported a series of cases here two years ago, I am prepared to say that in every case of untreated tabes the colloidal gold test will be found positive.

Dr. Joseph Collins, New York: My experience with the colloidal gold test in tabes has been the same as Dr. Sippy's so far. I am at this time not in a position to report upon it.

ADVANTAGES OF A PATHOLOGICAL CLASSIFICATION OF NERVE CELLS

WITH REMARKS ON TISSUE DECOMPLICATION AS SHOWN IN THE CEREBRAL AND CEREBELLAR CORTEX*

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Last year I brought before the Association a communication on the direction of research as to the analysis of cortical stigmata and focal lesions in certain psychoses.[1] Therein I essayed to present some reasons why the present neuropathological situation is not entirely hopeless, even when we approach the fundamental genetic problems of mental disease. I felt that there was much warrant for declaring that the stock of structural investigation, so far from having dropped below par, was indeed a very promising stock. My chief point was that, in the analysis of the cerebral cortex in mental disease, advantage must be taken of the transition planes between "sensory" and "psychic" tissues as provisionally defined by the modern cortex topographers,[2 3] for the purpose of observing the differential reactions of the so-called "sensory" and "psychic" tissues to identical conditions of a disturbing or noxious nature. For these adjacent zones of "sensory" and "psychic" tissue, whatever their embryogenesis or special physical and chemical natures, are as a rule under identical mechanical conditions (*e. g.*, of vascular

* Being contributions of the Massachusetts State Board of Insanity No. 121 (1915, 24).

Bibliographical Note: The previous contribution of the Massachusetts State Board of Insanity's series of scientific contributions was No. 120 (1915, 23) by E. E. Southard, entitled The Feebleminded as Subjects of Research in Efficiency, published in the Transactions of the 1915 meeting of the National Conference of Charities and Corrections held at Baltimore.

supply, of elasticity and pressure, of heat and the like), and may be safely conducted through the enormous gamut of physical and chemical change involved in modern microscopic technic under conditions so nearly uniform that without difficulty the "visuosensory" and "visuopsychic" tissues types, the "auditosensory" and "auditopsychic" tissue types, as well as many other contrasting types, can be observed under the selfsame coverglass. Of course the technical difficulties are greater in the way of comparing two coördinate portions of a given cortex type in the two hemispheres, since the technic of "total" brain sections, while suitable enough for fiber studies of an anatomical nature, is unhappily as yet not suited to the finest studies. However, much can be learned from a systematic comparison of tissue types in the two hemispheres as well as from a study of immediately adjacent cortex types. Perhaps I do not need to insist that the final truth or preciseness of the designations of cortex tissue as "sensory" and "psychic" is not involved in any question as to the value of studying these tissues, since it is safe to say that everyone is now agreed that at least some part of the mind is related with some part of the cortex and that all parts of the cortex are more or less directly related with one another.

Last year I presented a few examples to illustrate my general contention that so-called "sensory" and so-called "psychic" tissues may show a differential pathological reaction despite their adjacency and apparent subjection to identical physical and chemical conditions. My examples were, it may be recalled, from the comparatively well charted visual area (calcarine—"visuosensory," common occipital—"visuopsychic") and the somewhat less well understood common sensory area (postcentral gyrus, susceptible to a similar subdivision).

The conclusion is inevitable, whether or not my special contentions are in detail correct (notably my correlations between "visuopsychic" tissue gliosis and visual hallucinations and between gliosis of an area related to complex kinesthesia and the symptom known as catatonia,[4 5]) that the general contention must remain standing, to the effect that neuropathology has here a method which, however tedious and expensive, is surely rewarding to the

extent of showing something pathologically different in two closely adjacent areas under identical general vascular conditions.

This year I wish to animadvert in a still more general way upon the topic of *microlocalization* in the cortex. Whereas my argument may seem immediately foreign to the internistic aims of the members of this Association, yet I am convinced, (1) that the claims made are claims of a distinctively pathological (and not generally biological) method of study, and (2) that internists are those who do see, or should see, the value and applicability of such essentially pathological (medical) methods to such topics as modern psychiatry.

I know that I should by rights dwell a little on that portion of my title which speaks of the advantages of a "pathological classification" of nerve-cells. We pathologists (taking all physicians for the moment to be pathologists, as in a sense they are well-known to be) are nowadays too prone to regard our methods and classifications as biological and as without further specificity. One might as well, in the opinion of the writer, dispose of physiological methods in terms of physics and chemistry, or the method of physics as a compound of geometrical and phoronomic methods. However that may be, it seems clear that the pathologist has much interest, not only in those metric and statistical methods which modern biology employs, but also in what may be termed "survival values." The term "survival values" has a Darwinian ring and perhaps justifiably so. Yet when we are considering the survival value not of an organism but of parts of organisms, the simple Darwinian aspect of the conception alters. For we have in mind, not so much synthetic effects, as analytic effects. Gowers' conception of differential "abiotrophy" has something in common with the doctrine of distinct differential survival values. To be sure, the Gowers concept has rather more to do with certain tissues that as it were run out or run down than with tissues interfered with differentially by disease. The concept of abiotrophy is rather more a concept of primary or idiopathic ceasing of a tissue to thrive than a concept of a thriving actively stopped or blocked. In brief, the concept of survival values here discussed is rather more a matter of the internal economy of the multicellular metazoan than a matter of Darwinian survival of whole organisms. And, again, the concept

of survival is of survival, not merely in stable conditions (like the running of a clock until it stops) but in unstable conditions (like that of a clock stopped by some external force).

This is not the occasion to discuss the logic of methods in pathology or in neuropathology. It is sufficient to contend that tissues and cells apper to have differential vitalities and that these differential vitalities appear under the guise of a difference, not merely in what Bergson might call the *élan vital*, but also in the powers of resistance of the tissues or cells. Now the latter have not been sufficiently studied in the concrete, especially in neuropathology, despite the fact that neuropathology is supremely well characterized for such study on account of the variety of cells packed away in small geometrical units in the central nervous system. We should be able to study effectively the indices of resistance of nerve cells. A truly "pathological" classification of nerve cells might then be a classification of nerve cells according to their indices of resistance and survival under a variety of conditions. Naturally we are a number of years away from even the more obvious of such classifications. I wish to make it my present task to present a striking contrast in apparent survival value of various apparently homologous elements of the cerebral and the cerebellar cortex.

My conclusions naturally touch, in the present phase of neuropathology, only a few of the cellular elements of the cerebral gyrus and the cerebellar lamina respectively. Moreover, my conclusions as to the curious distinction in power of resistance between the large Betz cells of the precentral gyrus of the cerebrum and the large Purkinje cells of the cerebellar lamina is not founded on a thoroughgoing systematic study of the reactions of these cells under all known physical and biological conditions. A systematic study of a still more general nature is of course highly desirable, although it cannot be carried out in any existing laboratory with the funds at the disposal of neuropathology, a science in general almost inconceivably neglected. Perhaps I would best term my results "impressions" rather than "conclusions," based as they are upon observations confined to such effects of local hemorrhage, intoxication, exudation, and the like, as the natural experiments of human neuropathology permit.

Under ideal conditions, we should doubtless approach the matter of neurones from the geometrical side and describe and measure, name, and classify all available nerve cells in the major types of animals, including man. Such a task has been reasonably well carried out for the more easily available cells of the circulating blood. The necessity of executing a similar plan for fixed tissues has not appealed to the histologists to any convincing extent, and perhaps rather less so in neurology on account of the world's habit of postponing neurological work until other apparently simpler affairs are well in hand. Only of late has a classification of neurones from the standpoint of mechanics been attempted, and even such work as that of Dolley and Crile has suffered from the lack of fundamental metric work done by histologists. It is naturally difficult to evaluate the various metamorphoses of the Purkinje cells which Dolley and Crile are inclined to regard as of dynamic significance when so little is known as to the mechanical and physicochemical conditions under which nerve cells of all sorts must labor. Accordingly, it seems unsafe to draw extensive conclusions of a physiological or neuropathological nature from what we at present know of neurocytology, whatever opinion we may hold as to the objectivity of the Purkinje cell findings of recent American workers. There can be no doubt, however, that the Purkinje cell is a peculiarly feeble cell under a number of conditions which can be in part defined. There can be no doubt that Dolley, Crile, and their followers, have selected a cell of considerable lability; that is, a cell with a comparatively low index of resistance to at least certain disturbing or noxious influences.

I had occasion a number of years ago to observe the extraordinary lability of the Purkinje cells in some work on the neuroglia framework of the cerebellum in cases of marginal sclerosis[6] (1905), and again in some work on lesions of the granule layer of the human cerebellum communicated at the meeting of the American Association of Pathologists and Bacteriologists in 1906.[7] At that time I noted that Obersteiner,[8] so long ago as 1871, and Kirchhoff[9] in 1882, had described absence of Purkinje cells from atrophic areas in the cerebellum. In fact, in my second paper on the cerebellum above mentioned, I noted as a "familiar fact" that the great

elements of the Purkinje cell belt are the first to undergo destruction. Interest in those days was directed rather at neuroglia reactions than to essential changes in the Purkinje cells themselves. In that older discussion, I pointed out that in many types of lesions the Purkinje cell belt is the initial seat of activity, which activity takes the form of neuroglia cell overgrowth. The Purkinje cell layer must be in fact regarded as a *locus minoris resistentiæ*. In the present year I was pleased to observe in the course of some work[10] done in the Psychopathic Hospital Laboratory by Dr. Egbert W. Fell, the striking tendency to the deposit of fat (demonstrable by the Scharlach R method) in and about the Purkinje cells in cases of mental disease apparently due to intoxication or infection (the group of so-called "toxic" psychoses), although Dr. Fell was not able to discover similar intracellular changes in a variety of other more chronic conditions. There is good reason then why modern workers should choose the Purkinje cells of the cerebellum as a favorite field for the study of the effects of a variety of changed conditions.

The point of my present communication is that the large Betz cells of the precentral gyrus, taken as representing the motor cortex, are far less labile than the Purkinje cells. The likelihood that Betz cells would withstand relatively tremendous physicochemical changes was more or less consciously described in my paper of 1908 on the "Mechanism of Gliosis in Acquired Epilepsy."[11]

In casting up a program for the better development of neuropathological research, I could conceive no better program than the investigation of neurones from the standpoint of their differential lability. Expressed otherwise: What is the index of resistance? What is the vital capacity? What the viability or "survival value" of the different cells? In default of a complete geometric classification, in the absence of any signs of a phoronomic classification (indeed, such phoronomic classification is unlikely to have great scope in the cells of fixed tissues), in the prevalent feeling of grave doubt as to the virtues of a mechanical classification (whether this be taken from the standpoint of equilibrium or from a kinetic standpoint), we must turn perhaps to a more concrete method of classification. There are some signs of feasibility perhaps in the

tinctorial classification proposed by Nissl, although this eminent worker is far from considering his tinctorial classification as based on anything but what he terms "cell equivalents." Aside from this endeavor of Nissl, which logically derives from Ehrlich's proposal of methylene blue as an agent by which specific characters of cells might be observed, there are few or no traces of physical and chemical classifications in any stricter sense. Thus, should one inquire whether the elasticities of nerve cells have been studied or whether we know much concerning the effects of pressure upon nerve cells or the phenomena of their so-called "capillary" chemistry, we should find an almost Egyptian darkness to prevail. Something, to be sure, is known concerning the thermal metamorphism of cells, at least the disruptive and destructive effects of heat. The various other branches of physics have been very largely neglected by the neurocytologists.

To illustrate the difficulty of the situation, I have been accustomed to quote from Sherrington a laborious catalogue of changes which might occur at the synapses, which Sherrington himself defined.[12] In the light of this catalogue, which I give below, the condition of neurocytology might be regarded as a desperate one; still, if the physical possibilities of the synapses can be defined even to this degree, the outlook is really not desperate. The synapses, according to Sherrington, "might restrain diffusion, bank up osmotic pressure, restrict the movements of ions, accumulate electric changes, support a double electric layer, alter in shape and surface-tension with changes in difference of potential, alter in difference of potential with changes in surface-tension or in shape, or intervene as a membrane between dilute solutions of electrolytes of different concentration or colloidal suspensions with different sign of charge." Accordingly, what chance might a "pathological" classification of neurones possess? At first sight, a negative answer would be given by almost any biologist. Before attacking such a topic from the pathological point of view, should there not be a congress of specialists, if not in geometry and phoronomics, then at any rate in mechanics, physics, and chemistry, which congress should lay out a program of metric and quantitative work upon which conclusions of a pathological nature might properly at some future date be grafted?

In point of fact, the situation of the pathologists is not so hopeless. The pathologists' work need not be postponed. As I have elsewhere[13] and in a quite other connection been emboldened to state, pathology has its short cuts. It is perhaps a science of short cuts to biological conclusions. For example, it would be difficult to estimate how many decades it would have taken a congress of workers in physiology and in normal cytology, to discover the Virchowian principle, *omnis cellula e cellula*. From a study of exudation, Virchow was led to his interesting generalization after a comparatively brief period of work. Another instance may suffice from an entirely remote field. A tremendous impetus to the study of human character has beyond question been given by William James's *Varieties of Religious Experience*, a book which may be said deliberately to adopt the study of caricatures of character as the best means of coming at a reasonable notion of normal character types; at least, such I believe to be the trend of psychobiological study since the publication of that work. To be sure, the task of describing and evaluating character is (if possible) still farther from completion than the task of cellular biology in general and of neurobiology in particular.

The logic of pathology has nowhere been comprehensively studied so far as I am aware; even so gigantic a work as that of Wundt on *Logik*, written by a man of great physiological as well as psychological insight, fails to consider systematically this topic. It may well be, however, that the specific logic of pathology, as far as it is not identical with that of physiology, physics, and chemistry, is somewhat dependent upon the theory of survival values of cell units. The death point of a cell under varying conditions is a far more definite datum for study and interpretation than the majority of quantitative variations which the students of the normal histology, physiology, and the like are able to contribute.

However true or relevant all this may be, there surely does attach a certain intrinsic interest to studies in the death point of nerve cells. Take, for example, such a question as the nature of those almost entirely obscure mental diseases known as dementia precox and manic depressive psychosis, in the latter of which

diseases singularly little can be observed in the gross brain.[14] Let us suppose the indications of a special line of attack upon the histology of manic depressive psychosis (as presented in my communication[15] with Bond in 1914) to be sound. Still the pigmentation or lipoid deposits of the cells would remain merely quantitatively different from those found possibly under normal conditions or in conditions of senescence. Far more convincing here would be such results as those of Orton in his study of satellite cells in fifty selected cases of mental disease.[16] For the occurrence of satellite cells (so-called satellitosis) in the nervous system in increased number doubtless argues far more than the stationary changes that are normal to nerve cells, far more than mere alterations in the "self-supply" of their metabolism. In fact, perhaps satellitosis or neuronophagia may be regarded as definitely denoting a certain disappearance of elements or portions of elements normal to nervous tissue. At least such might be our best hypothesis in the light of the contentions of Weigert notably in his studies of the neuroglia[17] in 1895.

The contentions of my communication before the Association last year (as to satellitosis, or overgrowth of a certain kind of neuroglia cells in the so-called "visuopsychic" area when no such overgrowth was demonstrable in the immediately adjacent "visuosensory" area) are obviously based upon identical conceptions. To throw into sharp focus the importance of such a comparative study of death points of cell types in the cerebrum and cerebellum respectively, I will reproduce two diagrams of the neurone supply of the cortex cerebri and of the cortex cerebelli respectively, as used for some years in my undergraduate course in neuropathology. A diagram of a similar nature, involving other neurones, has been before published in a paper on the optic thalamus.[18] The principle of these diagrams was communicated by Dr. S. T. Orton and myself at the meeting of the American Association of Pathologists and Bacteriologists in 1913, but has remained unpublished.

Fig. 1 deals with the neurone supply to the cortex cerebri, and is largely based upon prevalent ideas as to the course of impulses in the cerebral cortex, taking the precentral gyrus as the best known tissue. The diagram enables one to dispense with the

schematic semi-diagrammatic pictures found in most text-books and based upon more or less thorough idealization of actual pathological conditions. The ideas expressed by the diagram follow rather more closely the ideas of von Monakow in his *Gehirnpathologie* of 1909 than those of other authors. The arrows indicate the possibility of numerous short cuts which may well correspond with short

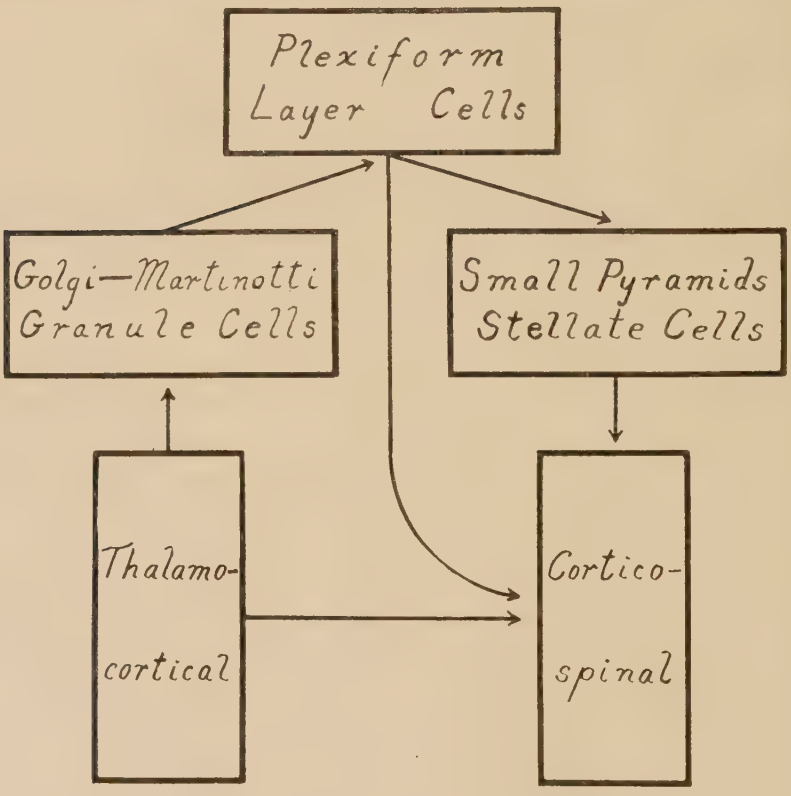

FIG. 1.—Neurone supply of cortex cerebri.

cuts actually used in function. The oblong unit containing the term "corticospinal" is of course the neurone whose cell body has long been known as the giant pyramid or Betz cell. If, now, an impulse passes through the "thalamocortical" unit so-called (the question of whether impulses run directly or by two or more units from the lower centres to the precentral gyrus is not essential

to the point at issue), then it may well be that sundry dendritic connections permit impulses to be passed directly into the Betz cell, as indicated by the arrow running from left to right from the unit named "thalamocortical" to the unit named "corticospinal." Possibly such a course of impulse is normal for certain relatively fixed and habitual neural processes. However, other paths are possible and, the higher the evolution of the animal, the more elements exist through which complicated paths may cut themselves. The majority of authors now consider that the granule cell layer or stellate cell layer divides the tissues of older evolution below from the tissues of more recent evolution above. It is regarded as an approximation of truth to say that the entire supragranular (suprastellate) system of paths may be regarded as related with higher functions. At any rate, various lower animals do not possess any truly supragranular tissue whatever, and possibly this fact is as good an index of their "inferiority" as any other.

Now it is clear that the corticospinal neurone (giant pyramid, or Betz-cell neurone) is in some ways the most important neurone in the precentral (motor) gyrus, since it is, as it were, the discharging neurone of said gyrus. If any impulses whatever can arrive at the corticospinal neurones, then some sort of action must result provided that the lower mechanisms are intact. Some sort of action or defensive manoeuver, whether of extension or flexion, whether a blow or a tremor, locomotion or static posture, must result. Let, however, the Betz cells be destroyed and the impulses that arrive or are initiated within the gyrus will fail of their effect, or will secure an effect through very devious paths. How important, then, may it well be to the economy of the organism that of all the cells of the gyrus, the giant cells shall possess the highest index of resistance! This the Betz cells seem to possess, at least so far as the fragmentary data now available can prove the point.

Let us now contrast conditions in the cerebral cortex with the somewhat simpler conditions of the cerebellar cortex. Fig. 2 deals with the much simplified neurone supply of the cerebellar cortex following some of the ideas of Ramón y Cajal. If we suppose that impulses arrive in the cerebellar lamina by way of the climbing fibers or moss fibers of Cajal, it is an easy speculation to conceive

that far more fixed and habitual reactions may be secured by way of the direct effects of the climbing fibers rather than by the mediated effects of the moss fibers. For the moss fiber neurones must by hypothesis send their impulse to the Purkinje cells by way of the granule cells.

On the score of function, it would seem that the giant cell of the cerebral cortex and the Purkinje cell of the cerebellar cortex must be homologous cells and together regarded as the discharging cells of their respective neurone complexes. It would be natural to suppose, then, that nature's neural economy might best be conserved by the maintenance of the Purkinje cells at a high index of resistance. Why should not the Betz cells and the Purkinje cells possess approximately identical indices of resistance?

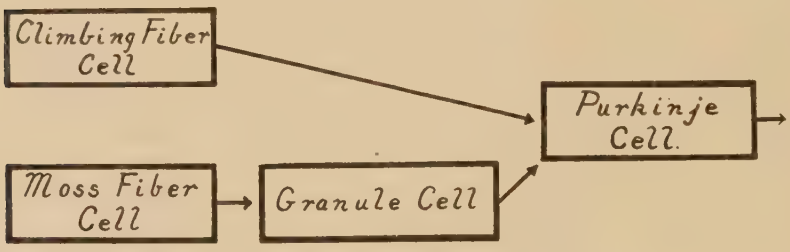

FIG. 2.—Neurone supply of cortex cerebelli.

Much research needs to be done along the indicated line, and it is clear that the earliest researches to be completed along these lines would very possibly deal with other elements roughly approximating in size the Betz cells and Purkinje cells. I do not wish to maintain that under all conditions which might be imagined the Betz cell is more resistant than the Purkinje cell. There may very well be differential physicochemical conditions in which the Betz cell would prove to be less resistant than the Purkinje cell. Nor is it my purpose here to explain in detail the evidence for the particular contention concerning the respective viabilities of these two cell types. The point has been sufficiently emphasized that there may exist such differential viabilities of important nerve cell types.

A word more as to the functional interest of the demonstration

of such viabilities. There seems to be little doubt that the supragranular (suprastellate) tissues are the point of attack in many cases of epilepsy. As I tried to express the matter in 1908, "The outer nerve layers tend, so to say, to *weather out* more readily than do the inner layers when under virtually the same conditions with respect to noxious agent." A number of cases in the study of gliosis in acquired epilepsy seem to support the conception that tissue destruction to a moderate degree may frequently leave the discharging apparatus intact when the inhibitory and controlling apparatus is destroyed.

If we should simplify (or as I now prefer to say "decomplicate") the tissue, we bring about the conditions for unimpeded discharge (a phrase of Hughlings Jackson). In the progress of convolutional atrophy in certain cases of epilepsy, the best conditions for lateral discharge from cell to cell seem to be produced so that we may well imagine that we may fail to demonstrate the existence of sufficient dendritic connections between the intact giant cells so that favorable conditions are produced for the so-called "march of convulsions."

Seeing that the small cells of the cortex have been removed by a process of "decomplication" and the phylogenetically older cells, the Betz cells, remain working, the precise condition is afforded for a sort of automatization of the cortex. In later work in connection with a study of the optic thalamus, I spoke of the simplification of the cortical tissues found in various cases of organic epilepsy as favorable to the march of convulsions, and spoke of the tissues as reduced to conditions not much more complex than those which prevail, say, in the spinal cord. "Impulses once initiated in the neurones of such a spinalized cortex ran off with the speed and inevitability of spinal impulses when upper inhibitors are cut off, and a kind of hyperkinesis, namely, the epileptic attack, ensues." To be sure, a great number of adjuvant hypotheses are necessary to the full explanation of epilepsy. Still, if the agents that simplify or "decomplicate" the convolutions in epilepsy were to simplify by means of destroying the Betz cells, or even by destroying all possibility of functional communication between Betz cells, then epilepsy might not exist. If the sort of thing were going on in the cerebral cortex which seems to go on under identical

conditions in the cerebellar cortex, then, by hypothesis, under these conditions epilepsy might not exist.

Let us turn to the cerebellar situation. Here, as we have stated, it is a familiar fact that the Purkinje cell layer is a *locus minoris resistentiæ*. As I pointed out in 1905, the macerating cerebellum in edema tends to split along this layer. There is in tuberculous meningitis and in epidemic cerebrospinal meningitis often considerable cell débris and edema in the layer. In tuberculous meningitis we not seldom find a focal destruction of Purkinje cells together with a loosening of structures adjacent, and in ischemic injury to the lamina, we may find a line of neuroglia cells in and near the Purkinje belt, as the only sign of reaction for a considerable distance on either side of the layer. A case of typhoid fever with small hemorrhages in the cerebellar pia mater, published in the granule layer study of 1907, offered a natural experiment to prove both the maximum lability of the Purkinje cells and the initial neuroglia activity of the Purkinje cell belt. Pictures consistent with these descriptions have been found from time to time in work since those earlier publications. Evidence seems to prove that in a great number and variety of conditions, particular laminæ of the cerebellum may be entirely closed off from neural function through the death of Purkinje cells despite the persistence of the other smaller cells of the lamina. It would seem that of two lesions which seem to decomplicate the cerebral and cerebellar cortex equally, the one leaves the Betz cells intact and the other destroys the Purkinje cells. The decomplication in the one case reduces the cerebral cortex to conditions of an automatic machine by a process we have named "spinalization;" in the other case, cerebellar function is "bottled up" through the destruction of the discharging elements of the lamina.

Of what advantage this distinction might be to the organism, it would be premature to say much. Nevertheless, it might be said that it would be of some general survival advantage to the organisms to preserve its Betz cells as long as possible, even if the remainder of the cortical apparatus were reduced to archaic conditions. In the case of the cerebellum, on the other hand, it might well be asked whether the function of the total neural mechanism might

not be still more unfavorably affected if the Purkinje cells were to persist when the granule cells were dead. The cerebellum in that event might seriously perturb the action of the neural mechanism by throwing unfortunate tonic, sthenic, and metric factors into a given functional situation. It seems to be generally thought that the cerebrum can get on fairly well without the cerebellum, and that in the higher organisms at least the cerebellum is of lesser value taken by itself. If the cerebrum has more of a function with respect to the sequence and succession of muscular events, then the cerebellum has more to do with the pattern and simultaneous correlation of muscular activity (tone, intensiveness, coördination, and the like). But if we may go farther and say that the cerebrum is itself also capable of undertaking with fair success the duties of coördination in space, then it is clear that the cerebellum is more of an adjuvant of the cerebrum than the cerebrum to the cerebellum. If this account is approximately true, then it might be of evolutionary value that the Purkinje cell should be blotted out under precisely the same conditions in which the Betz cell should be maintained.

We may add another point if we like to the effect that, so far as we know now, the cerebellar cortex is almost entirely uniform in its general structure throughout, and that at present no means exist of telling one lamina from another. If this is the case, then a gradual cerebellar destruction involving the Purkinje cells of a lamina or two might not interfere with the proper workings of the tonic and sthenic functions of the cerebellar cortex; for if only the Purkinje cells of a lamina are placed *hors de combat*, then by lateral conduction through numerous intact cell connections, impulses might reach intact Purkinje cells and thereby reach the dentate nucleus to be distributed safely enough to proper destinations. Perhaps, however, this latter speculation would better be entirely suppressed at the present time.

Enough has been said to show that neuropathological research:

1. Might do well to engage on a program of studying by available methods the differential viabilities of the various nerve cell types, thereby erecting an essentially "pathological" classification of nerve cells on the basis of their powers of resistance or survival values; and

2. Might endeavor to collect data as to the differential effects of simplification or "decomplication" of nerve tissues, having in mind the evolutionary or survival values of the functions which different forms of decomplication would destroy or leave intact.

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ERYTHROPHAGOCYTOSIS AND MYELOBLASTOSIS OCCURRING IN THE GENERAL CIRCULATION IN ASSOCIATION WITH HEMOGLOBINEMIA IN A PATIENT WITH PERNICIOUS ANEMIA IN WHOM A SPLENECTOMY HAD BEEN PERFORMED

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Numerous as have been the observations, intense as have been the investigations regarding the pathogenesis of primary pernicious anemia, our definite knowledge of this disease-condition is even less than meager. No generally acceptable proof has been offered as yet that the congener of symptoms which mark the condition is the result of pathogenic processes emanating in the blood, in the bone marrow, or in the spleen itself; or that its symptom-complex depends upon one or more pathogenic factors which involve one or more of these tissues in coördinated functional disturbances. Hypotheses have been presented in place of facts, none of which can fully explain the etiologic or the pathogenic features of this affection; none of which promises a cure of this so-called disease. Our treatment, therefore, has been based almost entirely upon empiricism, which leaves us today, as far as pernicious anemia is concerned, as helpless to check its course as were our predecessors in the time of Addison. While it is our duty to try all means, empiric though they be, in the hope of controlling this disease, it is our further duty to ignore such when based on suggestions of fanciful or illogical hypothesis.

The medical world is now engaged in deciding whether the surgical treatment by splenectomy, as suggested by Eppinger and

Decastello, is to remain as an advance in the treatment of pernicious anemia or whether it will also be relegated to that large collection of useless measures—the fate of so many measures which gave great promise to their introducers at least, but which signally failed in the hands of others.

In determining the value of surgical treatment one must be guided not by immediate but by end results. End results are unfortunately but rarely reported. It may be that the two years which have elapsed since the first splenectomies were done for pernicious anemia are too short a time to announce end results. Our final judgment of the value of this procedure will be formed when we learn of the fate of those patients who were subjected to this operation. Thus far it would seem from a review of the few cases of which end results have been published that splenectomy offers no more than does blood transfusion, medicinal agents, or even exposure to fresh air and sunlight.

The following report deals with an unusual blood picture in a patient who suffered from a pernicious anemia, and who died from an exacerbation of the disease eight weeks after a splenectomy, which had been immediately preceded by a blood transfusion. These procedures had been attended by an improvement in the symptoms of her disease; but whether the improvement was the result of the blood transfusion or whether the splenectomy was its factor cannot be determined; for it is a well known fact that blood transfusion alone done in patients with pernicious anemia is often followed by a definite, though temporary, change for the better, perhaps as often as is splenectomy.

Eva H., aged forty-three years, married; medical No. 149304; entered Mount Sinai Hospital on October 11, 1914, complaining of general weakness.

Family History. Parents dead; no member of her family had any condition resembling hers; negative as to newgrowths, cardiac or pulmonary disease.

Personal History. Menses began at fifteen years; were regular every four weeks, duration three days, flow moderate and without pain; two years ago they began to be delayed and infrequent, with marked irregularity, periods extending between six weeks and three months, with diminution of amount. She has given birth to six children, who, with the exception of

one who died of "summer complaint," are all living and well. She has had three miscarriages. The last menstruation occurred two months ago.

Past History. She remembers no other illness of any kind excepting a typhoid infection at the age of sixteen years.

Present History. One year ago she began to lose strength; she became easily fatigued after slight exertion, and when the day was finished she felt completely exhausted; shortness of breath and palpitation of the heart developed soon after, which were followed by severe headache and dizziness.

Four months ago she began to notice the gradual appearance of nausea associated with flatulence, gas eructations, pressure in the epigastrium, and a bad taste in the mouth; shortly after these symptoms vomiting appeared, though the vomiting lasted but three weeks, the vomitus consisting of poorly digested food not containing any blood; there has been no recurrence of the vomiting since then, though the belching has persisted. There has been and is constipation; her stools have not contained either blood or any segments of tape-worm.

Six weeks ago the weakness became aggravated and the skin of the body became of a pale yellow color; the cardiac palpitation became more disturbing and marked since which time the patient was compelled to keep to her bed. Following this the eye-sight grew poor, vision being blurred, "black spots and flashes like candles" appearing before her eyes. There was an accompanying "ringing and roaring" in the ears. Dizziness was now much more constant. There was no bleeding from the nose, the gums, stomach, or bowels. She lost six pounds in weight in the last four months.

Physical Examination. October 11, 1914. Patient medium-sized, adipose well marked and generally distributed; apparently well-nourished.

Skin: Lemon-colored, no eruption; no petechiæ, no ecchymoses.

Mouth: Teeth contain many fillings; artificial teeth-inserts in plate in lower jaw; remainder of teeth deformed. Tongue clean and moist. Soft palate, pale yellowish color. Tonsils small.

Superficial lymph nodes: None palpable.

Thorax: Emphysematous in type.

Lungs: A moderate degree of emphysema present, otherwise negative.

Heart: The upper border, third rib; right border, left sternal margin; left border, midclavicular line; apex in the fifth interspace. Sounds of good force and quality, with a systolic murmur heard at apex and transmitted to base; second pulmonic accentuated; systolic murmur at aortic area with second aortic accentuated; action rapid and regular; radial pulses equal, rapid, regular, not easily compressible; no definite sclerosis.

Abdomen: Pendulous; generally tympanitic; spastic cecum and sigmoid.

Liver: Upper border, fifth interspace, lower border is felt 1 cm. below the free costal margin, the edge being rounded.

Spleen: Edge firm and sharp, felt 2 cm. below left costal margin.

Extremities: Slight edema of the feet, does not extend above ankles; crests of tibiæ irregular; marked percutory tenderness over both shins, as also over lower sternum; hallus valgus; varicose veins in skin of both legs.

Reflexes: Patellar normal.

No anesthesia or other sensory disturbances. No motor disturbance such as paralysis or paresis.

Pelvis: Uterus freely movable, retroverted; tubes and ovaries palpable; no abnormalities. Rectum: Dilated.

Blood Examination: Hemoglobin, 40 per cent.; red blood cells, 1,280,000, color index, 1.5. The red blood cells show slight poikilocytosis, anisocytosis and a polychromasia; in the count of fields of the smear containing 200 white blood cells three normoblasts were found; white blood cells, 8000; polynuclears, 80 per cent.; small lymphocytes, 20 per cent.

Gastric Contents: One hour after the usual test meal only 7 c.c. were obtained, the contents being fluid, with partly digested food; no macroscopic blood; this showed a total acidity of 10, free HCl, 0; there was no lactic acid and no Boas-Oppler bacilli present. There was no pepsin and no rennin. Microscopically no red blood cells were found.

The patient was put on iron-free food in order to estimate the amount of iron excretion. The twenty-four-hour stool of October 16 showed 13.2 mgr. of Fe, and the total urine for the same period showed 1.2 mgr. of Fe; the analysis of the ingested food for the same period gave 4.48 mgr., hence the Fe excretion in stool and urine (14.4 mgr.) less the food Fe 4.48 mgr. showed that the endogenous Fe elimination was 9.92 mgr.

The subsequent analysis of the stomach contents showed a persistent total achylia, and examinations of the stools for ova and parasites were negative; benzidin and guaiac tests were negative in the feces.

October 17. The patient complained of a peculiar paresthesia in the soles of her feet; sensory tests showed no deviation from the normal in regard to thermic, tactile, and pain impressions; nor could any evidence of any ataxia be elicited.

The urine examination on her admission gave no evidence of any renal disturbance; its sp. gr. 1020; acid; amber; contained neither albumin nor sugar; no casts; bile was not present, but a marked reaction for urobilin was demonstrated.

The patient showed at this time no fever, the temperatures

extending between 99° F. and 100° F.; pulse rate 88; respiration 24. Wassermann test was negative. Urobilinogen was demonstrated today in the feces. The patient left the hospital two days later (October 19), against advice, but returned the next day.

Examination of the retinæ showed no hemorrhages, no change in the papillæ or disks. During the next four weeks the condition of the patient showed a steady deterioration. The skin became more pronouncedly lemon-yellow, the urine and feces contained larger amounts of urobilin and urobilinogen, respectively, the achylia gastrica was persistent, a glossitis developed, weakness became accentuated and the blood, in addition to an increasing loss of hemoglobin and a further reduction in the number of red blood cells gave the typical histological picture of a pernicious anemia; the latter merits some detailed attention, which may be obtained from a study of the annexed chart.

BLOOD EXAMINATIONS

	October 17		October 20	
Hemoglobin	33	per cent.	32	per cent.
Red blood cells	1,600,000		1,270,000	
Color index	1.3		1.3	
White blood cells	6,000		6,500	
Polymorphonuclears	72	"	71	"
Small lymphocytes	27	"	28	"
Large lymphocytes	...		none	
Eosinophiles	1	"	none	
Basophiles	...		1	"
Normoblasts	2		none	
Megaloblasts	none		none	
	The red cells showed the same degree of poikilocytosis, anisocytosis and polychromasia as on the first examination.		Slight anisocytosis, slight poikilocytosis.	

	October 27		November 8	
Hemoglobin	32	per cent.	26	per cent.
Red blood cells	1,290,000		1,110,000	
Color index	1.3		1.2	
White blood cells	8,600		6,000	
Polymorphonuclears	80	"	80	"
Small lymphocytes	16	"	16	"
Large lymphocytes	3	"	3	"
Basophiles	1	"	Eosinphiles 1	"
Normoblasts	1		3	
Megaloblasts	none		none	
	Macrocytes are abundant, very few microcytes, and poikilocytosis is slight.		Moderate amount of changes in form and size of the red blood cells.	

Owing to the progressive diminution of the hemoglobin and the number of red blood cells, a transfusion and subsequent splenectomy were determined upon; therefore on November 14, 1914, a syringe method transfusion was carried out, the hemoglobin being raised to 45 per cent., about 350 c.c. of compatible blood having been introduced. The next day the blood examination showed a rise in hemoglobin to 50 per cent., the red blood cells 2,040,000, the white blood cells 12,400, of which the polymorphonuclears were 78 per cent., the small lymphocytes 18 per cent., the large lymphocytes 3 per cent., and the basophiles were 3 per cent.

On November 16 a splenectomy was performed by Dr. A. A. Berg with gas and ether anesthesia. The operation lasted thirty-five minutes. The spleen was found to be enlarged to twice the normal size, its surface was somewhat uneven, adhesions binding it to the stomach and colon; the vessels were greatly dilated, their walls being very thin. The adhesions were divided, the splenic vein being ligated and cut before the artery was submitted to the same procedure.

While there had been a sharp reaction following the transfusion, the temperature of the patient rising to 104° F., at the time of the splenectomy the temperature had not returned to normal; it did so on the fourth day following the operation; for the next ten days the temperature ranged between 99° F., and 102° F., following which the daily range was between 98.3° F. and 100° F.

Annexed are the summaries of the subsequent blood examinations:

	November 17	November 20	November 21
Hemoglobin	55 per cent.	45 per cent.	39 per cent.
Red blood cells	2,010,000	2,220,000	2,100,000
Color index	1.4	1.0	0.87
White blood cells	12,600	8,200	11,000
Polymorphonuclears	89 "	78 "	81 "
Small lymphocytes	7 "	18 "	15 "
Large lymphocytes	4 "	6 "	4 "
Eosinophiles	none	none	none
Basophiles	none	none	none
Normoblasts	2	none	2
Megaloblasts	none	none	none

	November 22		November 24		November 27	
Hemoglobin	40	per cent.	38	per cent.	40	per cent.
Red blood cells	2,120,000		2,012,000		2,100,000	
Color index	0.95		0.9		0.9	
White blood cells	9,200		10,100		8,400	
Polymorphonuclears	74	"	76	"	72	"
Small lymphocytes	24	"	23	"	25	"
Large lymphocytes	2	"	1	"	3	"
Eosinophiles	none		none		none	
Basophiles	none		none		none	
Normoblasts	1		none		none	
Megaloblasts	none		none		none	

	December 4		December 10		December 16	
Hemoglobin	40	per cent.	42	per cent.	48	per cent.
Red blood cells	2,210,000		2,110,000		2,080,000	
Color index	0.9		1.0		1.2	
White blood cells	9,600		10,200		13,100	
Polymorphonuclears	72	"	74	"	68	"
Small lymphocytes	25	"	24	"	24	"
Large lymphocytes	3	"	2	"	4	"
Eosinophiles	none		none		none	
Basophiles	none		none		none	
Normoblasts	1		none		none	
Megaloblasts	none		none		none	
					Sodium cacodylate given.	

	December 25		December 30	
Hemoglobin	48	per cent.	50	per cent.
Red blood cells	2,660,000		2,360,000	
Color index	0.9		1.1	
White blood cells	12,100		12,800	
Polymorphonuclears	71	"	65	"
Small lymphocytes	25	"	33	"
Large lymphocytes	4	"	2	"
Eosinophiles	none		none	
Basophiles	none		none	
Normoblasts	none		none	
Megaloblasts	none		none	

In all these examinations the only change which was definite was the permanent decrease in the macrocytic forms of the red blood cells; microcytes were particularly few in number. From a study of these counts it will be seen that there was almost a complete absence of the usual marked reaction which the bone marrow manifests after the removal of the spleen. The white blood cells have apparently increased in number. The improvement in the blood shows itself in the increase in hemoglobin, in the larger number of red blood cells, in the absence of nucleated forms, in the marked diminution in the macrocytosis and the microcytosis, and in the disappearing poikilocytosis. A peculiar feature which is worthy of notice is the entire lack of eosinophiles and basophiles following the splenectomy.

"The spleen on microscopic investigation showed an extreme degree of congestion everywhere in the sinuses and interstitial spaces; the reticulum was delicate and its cells were widely separated from one another by blood.

The Malpighian bodies were small and showed a marked degree of hypoplasia. The central arteries of the Malpighian bodies showed a narrowing of their lumen, either due to a proliferation of the endothelium or to a thickening of the hyaline intima; some of the Malpighian corpuscles show at their centre a slight degree of hyaline change. There is very little deposit of pigment. No myeloid elements were seen (Dr. W. Thalhimer).

A chemical analysis of two pieces of the removed spleen showed, in one piece, which weighed 68 grams, 25 mgrms of iron, or 0.03677 per cent., and in the other piece which weighed 69 grams, 25.48 mgrms. of iron, or 0.03688 per cent. (Dr. Kuttner). Extracts from the spleen showed no hemolysins.

The oxygen content of the blood was estimated on December 4, and found to be 0.518, and on December 17, 0.440 of normal O content.

Urobilin remained markedly positive in stools and urine.

The patient improved in general well-being after the splenectomy and after the immediate effects from the operation had passed, gained in weight, in appetite, and in strength, to the extent that she was reënabled to walk about and was no longer bed-ridden. It should be said that a part of the treatment consisted in keeping the patient in the open air during day and night. The yellow color of her skin disappeared, her cheeks assumed a pink tinge and the mucous membranes of her mouth and conjunctivæ lost their pallor. She left the hospital on December 31.

After her return to her home she remained in fairly good health, "better," she said, "than I had been for at least one year before." The improvement lasted, however, only for another three weeks after her return home, when the same weakness and pallor rapidly returned, the weakness became extreme, dizziness and cardiac palpitation recurred, associated with syncopal attacks, which were frequent. The patient was induced, therefore, to return to the hospital on February 4, 1915, in a condition much worse than ever before.

Physical Examination: Great pallor of mucous membranes; skin, more markedly lemon-yellow than before, considerable loss of hair since previous observation.

Heart: Left border, 1 cm. outside of left midclavicular line; soft, blowing murmur at apex, heard also over aortic area and over the vessels of the neck.

Liver: One c.c. lower than at previous examination, its edge being 3 c.c. below the costal margin, firm and rounded.

There is a thrombosis of the superficial vein of the right leg which is irregularly tortuous, and is surrounded by an ecchymotic area about 10 c.c. in its greatest width; the vein is tense, firm, and cord-like; it extends to the knee, and is tender over its whole length.

Blood examinations:

	February 4		February 6	
Hemoglobin	36	per cent.	34	per cent.
Red blood cells	1,776,000		1,536,000	
Color index	1.0		1.1	
White blood cells	40,800		42,000	
Polymorphonuclears	68.5	"	65.5	"
Small lymphocytes	25	"	25	"
Large lymphocytes	6	"	6	"
Eosinophiles	0.5		0.5	
Basophiles	none		none	
Normoblasts	numerous		numerous	
Megaloblasts	numerous		numerous	
Myelocytes	none		0.5	
Large mononuclears (myeloblasts)	none		2.5	

In the white blood count here stated it must be borne in mind that it included the many normoblasts and megaloblasts which the blood now contained. There were in addition many small deeply stained macrocytes and microcytes, the rest of the red blood cells showing a marked anisocytosis, but only slight poikilocytosis. A few of the normoblasts show basophilic stippling. Myelocytes and large mononuclear forms appear in the specimen of February 6, for the first time.

Compared with the counts made on her previous stay in the hospital, the blood shows a loss of hemoglobin, a diminution in the number of red blood cells, and particularly a very marked increase in the white blood cells, with a small myelocytic content.

Feces: No microscopic evidences of blood; no ova; no parasites. Urobilinogen present.

Gastric contents: Nothing was obtained from the test meal. When another attempt was made on the next day, a raisin test meal having been given, the amount recovered was 25 c.c. of poorly digested food, containing no raisins, whose total acidity was 4, free Hcl absent, no bile, no lactic acid,no blood, no rennin, no pepsin (Dr. B. Crohn).

Urine: Acid; 1014; no albumin; no casts; urobilin positive; microscopic, a few white blood cells, and epithelium.

Temperature, 99° F.; pulse, 88; respirations, 24.

From the day of her last admission the patient speedily declined: the breathing became more difficult; the color became much paler; the pulse rate rose to 104; the heart sounds became feebler and more distant; assum-

ing the embryocardial rhythm; restlessness and air hunger developed, with both inspiration and expiration labored, and the temperature rose to 103° F.

The chemical examination of the blood during this period showed the oxygen content to be 51.4 per cent. of the normal, the CO_2 to be 2.53 times greater than normal, containing 10.61 per cent. (Dr. Bookman.) Cholesterin content, 0.155 per cent. (Dr. Rothschild), about the normal amount. Wassermann was again negative.

On February 10, a definite and marked change for the worse developed. The pallor was extreme; delirium supervened; an acetone odor was detected in the breath, and the pulse became imperceptible. It was determined to do a transfusion and a donor was sought. In the meantime on the morning of this day another blood examination was made, with the following results:

February 10, 1915, 9.30 A.M.

Hemoglobin	13	per cent.
Red blood cells	676,000	
Color index	1.0	
White blood cells	82,400	
Polymorphonuclears	64.6	"
Small lymphocytes	16.3	"
Large lymphocytes	5	"
Eosinophiles	0.3	
Basophiles	none	
Large mononuclears	1.6	"
Neutrophile myelocytes	6.6	"
Basophile myelocytes	0.3	"
Myeloblasts	5	"
Normoblasts	numerous	
Megaloblasts	moderate number	

There were very many normoblasts and only a moderate number of megaloblasts; marked anisocytosis and polychromasia. The red cells contained many reddish small staining bodies in their protoplasm, Howell-Jolly bodies, and nuclear ring remnants. Almost all the normoblasts showed basophilic stippling.

Blood was taken for tests for the purpose of obtaining a compatible donor's blood, and this blood showed in the container a marked laking or hemolysis, the serum being very deeply red stained. The urine passed just before this specimen showed a decided hemoglobinuria; this coexisting hemoglobinomia and hemoglobinuria had developed over the night of February 9.

A suitable donor having been obtained, preparations were undertaken to perform the transfusion, but while they were being carried out the patient died.

The last examination of the blood was made at 9.30 P.M., February 10, 1915, one hour before death.

February 10, 1915, 9.30 P.M.

Hemoglobin	11	per cent.
Red blood cells	608,000	(of this number, there were 94,080 nucleated cells)
Color index	0.91	
White blood cells	168,000	(which was the sum total of *all* nuclear forms estimated in the counting chamber, of which 73,920 are white blood cells and 94,080 are red blood cells with nuclei).

A blood-smear count was made and 1403 nucleated cells, including red and white blood cells, were individually examined and counted; of these 503 were normoblasts and megaloblasts, and 900 were cells commonly included under the white cells. A detailed summary of this follows:

		Per cent.	Absolute count	
Red cells:	Normoblasts	....	464	
	Megaloblasts	....	39	
				503
White cells:	Polymorphonuclears	54.3	488	
	Lymphocytes	23.3	210	
	Eosinophiles	1.1	10	
	Basophiles	0.1	1	
Myelocytes:	Neutrophilic	11.9	105	
	Eosinophilic	0.5	5	
	Basophilic	0.1	1	
Myeloblasts:	Myelogones of Klein	8.5	74	
Phagocytic cells:	Polymorphonuclear	....	1	
	Myelocytes	....	2	
	Myeloblasts	....	3	900
	Totals	99.8	1403	

These painstaking counts were made by Dr. Rosenthal, a member of the house staff, who deserves great credit and this personal expressions of thanks.

The microscopic examinations of the blood on this day gave a picture more like that of a smear from the bone marrow than that of circulating blood. It showed the rare phenomenon of a phagocytosis occurring in the peripheral blood, which was participated in by polymorphonuclear leukocytes, by myelocytes and by those peculiar large mononuclears, some of the size of the macrophages and megacaryocytes of the bone marrow, which are looked upon as primordial cells, and which are here called "megaloblasts," and which Klein has termed "myelogones." The phagocytic cells contained one, sometimes two, and in one of them which I saw, three red blood cells in their cytoplasm. In addition to the large number of white blood cells, which included many of the young cells of the granular group, there was an unusual large number of the nucleated forms of the red cells, which constituted the larger portion of the total count of nucleated white cells, as may be seen

from thesummary. The red cells showed a most accentuated degree of polychromasia, with numerous Howell-Jolly bodies. The platelets seemed to be much increased, though, much to my regret, no count of them was made. The entire picture indicated a tremendous activation of the bone marrow, both of its erythroblastic and leukoblastic elements, which caused primordial and immature forms of cells to be thrown into the general circulation.

While a myelocytosis is not uncommon in the blood of patients suffering with pernicious anemia, the unique feature of this case is the presence in the circulating blood of the primordial forms, the myeloblasts, of which the larger forms have the general structural and tinctorial characters of the cells which Klein calls "myelogones." The other important feature of interest in this case is the hemolysis which took place in the circulation and which gave rise to the hemoglobinemia and the hemoglobinuria, features which a fairly diligent search of the literature failed to disclose as occurring in pernicious anemia.

Phagocytosis of red and white blood cells in the peripheral circulation has been reported, exceptionally it is true, particularly after transfusions of blood, and in the anemias associated with the leukemias. Thus in a case reported by Dr. J. Gardner Hopkins from the service of Dr. T. C. Janeway in St. Luke's Hospital, New York City, under the title of "Phagocytosis of the Red Blood Cells after Transfusion,"[1] in which there was a severe anemia resembling the primary pernicious type, the blood smear taken after the patient had undergone a transfusion of blood, showed great numbers of polymorphonuclear neutrophile leukocytes containing from one to six red blood cells in their cytoplasm.

W. B. Bartlett[2] records the history of a patient who suffered with cardiac disease accompanied with fever, in whom blood drawn from the ear lobes showed a leukocytosis varying from 30,000 to 300,000, but from blood obtained from the skin over a toe showed only 7,600 leukocytes. In the smears from the leukocytotic blood from the ear lobes numerous atypical mononuclears were seen of which many were phagocytitic, particularly to other leukocytes,

[1] Arch. Int. Med., 1910, vi, 270.
[2] Boston Med. and Surg. Jour., 1907, clvi, 629.

more rarely to lymphocytes and red blood cells. None of these mononuclears could be found outside of the skin of the ear lobe. Mary W. Rowley[1] published a report of this case of Bartlett with photographs.

F. Van Nuys[2] records the history of a patient with edema of the feet and who was suffering with a tape-worm, in whom the liver and the spleen were both greatly enlarged, and who also had aortic disease, in whose blood were found a large number of basophilic phagocytic cells capable of ameboid motion. In all probability the case was one of atypical leukemia. Connal,[3] drew attention to auto-erythro-phagocytosis occurring in the peripheral blood of some patients in West Africa who suffered with certain forms of protozoal diseases.

Considering the fact that myelocytosis and myeloblastosis have occurred in individuals in whom the spleen had not been removed, it would seem a logical inference that the absence of the spleen in this patient may not have been the important factor in the production of the unusual blood condition. It seems very likely that some agent acting independently of the spleen was the activating force in the bone marrow, either directly as a direct pathogenetic agent or indirectly as a destructive agent to the red blood cells. With the loss of these active oxygen carriers, the bone marrow may have responded partly to the deprivation of oxygen supply by developing new oxygen carriers in immature nucleated forms of red blood cells.

Another noteworthy feature of this case is the lack of immediate response on the part of the bone marrow to the removal of the spleen. It has been shown experimentally by Pearce and his co-laborers that when the spleen is removed in animals an increase in the red blood cells in the circulation soon follows. The same phenomenon has also been reported as occurring in the human subject when splenectomy had been performed. This patient after the splenectomy showed no appreciable increase in the number of the red blood cells even one and a half months after the spleen had been removed. This might justly be considered as a factor opposing Klemperer's

[1] Jour. Exper. Med., 1908, x, 78.
[2] Boston Med. and Surg. Jour., 1907, clvi, 390.
[3] Jour. Path. and Bact., 1912, xvi, 502.

view that the absence of the spleen is an activator to the bone marrow, or rather that the spleen serves as an inhibitor to the blood-producing function of the bone marrow.

Added factors in this case to the destruction of the red blood cells which is supposed to occur in the spleen and liver of all cases of pernicious anemia were the phagocytosis which took place in this patient's general circulation, and the destruction by lytic process which is almost unknown in this disease, viz., in the dissolution of the red blood cells in the bloodvessels thus producing the hemoglobinemia. These processes will probably account for the tremendous loss in the red blood cells occurring between February 6 and February 10, from 1,536,000 per cm. to 608,000 per cm.

It seems very likely that the same agent which activated the erythroblastic elements also perverted the function of the leukoblastic elements of the bone marrow in this case as shown by the presence of the unusual forms of the white blood cells which appeared at the same time in the circulation.

It is greatly to my regret that an autopsy could not be obtained. It might have been instructive to have seen whether spleniculi and hemolymph nodes developed to take on the function of the ablated spleen; and whether the blood in the portal circulation showed any differences from that in the periphery.

DISCUSSION

Dr. Joseph L. Miller: It is very hard to determine why splenectomy should help these cases of pernicious anemia. As Dr. Brill has shown by his case reported here, removal of the spleen does not remove the hemolytic agent. The good that is done seems to inhere in a stimulation of the resistance of the cells and a stimulation of the bone marrow, so that the blood recovers somewhat in spite of the hemolytic agent. I have in mind a case in which there were progressively increasing spinal-cord lesions after splenectomy, thus further indicating the retention of the hemolytic agent.

Dr. R. C. Cabot: We have now had six cases of pernicious anemia in which splenectomy has been done in the past few months. The operation was originally undertaken without hope of cure and without much hope

of remission; but the first cases did so well that the others were brought in on account of that experience.

No marked improvement could be noted in the first two or three weeks after splenectomy, then there was a rapid rise in the cell count, more rapid than that which may be noted in a spontaneous remission or after treatment by transfusion or salvarsan. All of the cases have gone above 4,000,000 in the cell count. Four out of the six patients are now at work, whereas before the operation they were entirely helpless. Of course, the blood still shows very definite changes.

Dr. N. E. Brill: Metabolism studies in my cases of pernicious anemia reported here showed no difference in iron elimination before and after splenectomy. With better protection of cells and greater production after splenectomy, it stands to reason there should be a retention of blood. Lecithin is known to protect blood cells, but in my case there was no increase of lipoid in the blood after splenectomy.

THE CLINICAL DIAGNOSIS OF ACUTE LEUKEMIC STATES

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Thanks to the gradual extension of hematological and histological technic, our conceptions of the leukemic states, acute and chronic, and of certain other conditions resembling them, are becoming more clearly defined. We have come to understand a leukemic state as one in which there is in the body definite proliferation of the leukopoietic tissues, either myeloid or lymphadenoid, and the appearance in the blood of immature white-blood cells, usually in large numbers, the degree of immaturity being the more pronounced as the cases are more acute.

This definition of leukemia excludes Hodgkin's disease and the ordinary leukocytoses and lymphocytoses, since in these processes neither the blood picture nor the changes in the tissues characteristic of leukemic states are present. It also excludes the aleukemic lymphadenoses and the aleukemic myeloses in which, though the histological changes in the hemopoietic tissues may be identical with those of leukemia, the characteristic blood picture is absent. It is very probable, however, that the aleukemic lymphadenoses and aleukemic myeloses are closely allied to the leukemic states for we have a great deal of evidence that acute leukemic states are often preceded by aleukemic stages; moreover, in the course of an outspoken leukemia, the hematological picture may change to that of an aleukemic state.

There is good reason for separating a group of acute leukemic

states from the chronic leukemic states, for the mode of onset, the clinical symptoms, the course, the duration, the blood picture, and at autopsy the histological changes, differ. Whether the etiological agent is the same for the two groups of cases we do not know. It is possible that they are identical though many investigators believe that the etiological agents are entirely different from one another. In favor of the identity of etiology is the fact that a chronic leukemia may have an acute onset or an acute termination.

With the majority of clinicians we divide the acute leukemic states into two great groups: (1) the acute lymphadenoid leukemic states and (2) the acute myeloid leukemic states, or if preferred, the designations: (1) acute leukemic lymphadenosis and (2) acute leukemic myelosis may be employed. The clinical course is very similar for the various acute leukemic states, but the blood picture of the acute leukemic lymphadenosis is sharply separable from that of acute leukemic myelosis, and, furthermore, the histological findings at autopsy in the cases that have been carefully studied and reported are specific. There are undoubtedly cases in which the blood picture alone may leave one in doubt as to which group the case belongs, though if the newer methods of staining be employed, and especially if the ferments in the leukocytes be studied, it is nearly always possible from the blood picture alone to give the case its proper nosological position. It is highly desirable, however, that wherever possible the clinical diagnosis should be controlled by histological findings as this disease is practically always fatal.

The greatest difficulty lies in deciding in a case in which all the cells are non-granular, and about the size of large lymphocytes, whether we have to deal with a large-celled lymphadenoid leukemia or with a small-celled myeloid leukemia due to the presence of micromyeloblasts. A careful study of the exact morphology and the staining reactions of the cells will usually suffice to distinguish, especially if the oxydase reaction and the indolphenol blue synthesis be used as controls. It is erroneous to think that cases in which the lymph glands are markedly enlarged are necessarily instances of lymphadenoid leukemia, just as it is wrong to assume that marked enlargement of the spleen without enlargement of the

lymph glands necessarily indicates that the leukemia is myeloid in origin. The lymph glands are often markedly enlarged in acute myeloid leukemia, and the spleen or the bone marrow may be predominantly involved in cases of leukemia which are not of myeloid origin. If an enlarged lymph gland be removed during life and subjected to careful histological study a decision could probably be certainly arrived at, for the lymphadenoid hyperplasia of acute lymphadenoid leukemic states is wholly different from the myeloid metaplasia met with in the acute myeloid leukemic states.

The object of the present paper is, however, not the discussion of the etiology of leukemia or a description of the pathological histology of the disease, but rather the presentation of an epitome of the blood findings and clinical symptoms in a series of acute leukemic states which have come under our observation. Our material includes some twenty-one instances of acute leukemic states, most of which have been studied in the medical service of the Johns Hopkins Hospital, though a few of them have been placed at our disposal by physicians in neighboring hospitals or by private practitioners. It is not our purpose to report all of these cases in full at this time, but in the lantern slides which are thrown upon the screen we shall present the blood picture in a dozen cases illustrating certain acute leukemic states proper and also acute stages in chronic forms of leukemia. We shall also refer to a case of atypical acute myeloid leukemia in which the blood picture closely resembled that of pernicious anemia, and also to a case of lymphemia apparently due to infection in which the blood picture might at first be taken for that of leukemia, but which we have not yet proved is associated with leukemic changes in the tissues.

Case I.—*A case representing an acute onset in a chronic lymphadenoid leukemia, the symptoms and the blood picture being of the acute type.*

F. B., aged sixty-five years, studied by courtesy of Dr. T. R. Boggs.

Clinical. Chills; sweats; fever; pallor; marked enlargement of all lymphatic glands; palpable spleen. Later, these acute symptoms declined and the disease became chronic.

Duration. The acute symptoms lasted about four months.

Blood.

Red-blood cells	4,048,000
White-blood cells	182,000
Hemoglobin	62.0 per cent.
Polymorphonuclear neutrophiles	4.4 "
Polymorphonuclear eosinophiles	0.0 "
Polymophonuclear basophiles	0.0 "
Lymphocytes	52.0 "
Fragile lymphocytes	43.6 "
Large mononuclears	0.0 "
Transitionals	0.0 "
Myelocytes	0.0 "

The blood picture was characterized in the acute stage by a high percentage of young, fragile cells.

CASE II.—*A case representing an acute stage in a chronic lymphadenoid leukemia, followed by a leukopenic stage.*

R. S., aged two and one-half years. Johns Hopkins Hospital.

Clinical. Continuous fever; anemia; marked enlargement of all lymph glands, spleen, and liver. Remission.

Duration. The high white count (50,000 to 8500) continued for two weeks, after which the white count varied between 6100 and 4800.

Blood.

Red-blood cells	2,200,000
Hemoglobin	30.0 per cent.

Differential count in the leukopenic stage:

Polymorphonuclear neutrophiles	7.3 per cent.
Polymorphonuclear eosinophiles	0.6 "
Polymorphonuclear basophiles	0.0 "
Large mononuclears	3.0 "
Transitionals	1.2 "
Neutrophilic myelocytes	0.6 "
Lymphocytes, large	81.1 "
Lymphocytes, small	6.2 "

The blood at this stage is similar to that in aleukemic lymphadenosis.

CASE III.—*A case of acute lymphadenoid leukemia with many large lymphocytes in the blood.*

M. H., aged thirty-two years.

Clinical. Sudden onset; fever; marked anemia; hemorrhagic diathesis; general glandular enlargement.

Duration. From symptoms three weeks, from diagnosis ten days.

Blood.

White-blood cells	60,000–70,000
Polymorphonuclear neutrophiles	4.4 per cent.
Polymorphonuclear eosinophiles	0.4 "
Polymorphonuclear basophiles	0.2 "
Lymphocytes	92.6 "
Large mononuclears	1.2 "
Transitionals	0.4 "
Neutrophilic myelocytes	0.8 "

Acute condition suggested by the large type of the lymphocyte present.

CASE IV.—*A case of acute lymphadenoid leukemia.*

A. B., female, aged twenty-one months. Johns Hopkins Hospital.

Clinical. Acute onset; septic temperature; progressive anemia; marked enlargement of all glands, liver, and spleen.

Duration. Death three weeks after onset of symptoms, two weeks after the diagnosis was made.

Blood.

Red-blood cells	2,300,000
White-blood cells	267,000–171,000
Hemoglobin	30.0 per cent.
Polymorphonuclear neutrophiles	4.6 "
Polymorphonuclear eosinophiles	0.2 "
Polymorphonuclear basophiles	0.0 "
Lymphocytes	92.4 "
Large mononuclears	1.2 "
Transitionals	0.0 "
Neutrophilic myelocytes	1.6 "

The blood picture is that of typical acute lymphadenoid leukemia of the large cell type with many (13 per cent.) large pathological forms. The few myelocytes present are of the mature type indicating a slight irritation-myelocytosis.

CASE V.—*A case of acute lymphadenoid leukemia with terminal leukopenia.*

B. K., child, aged eighteen months, a patient of Dr. John Ruhräh.

Clinical. Fever; rapid anemia; practically no glandular enlargement; spleen just palpable.

Duration. Death three months after appearance of symptoms; diagnosis two and one-half months before death.

Blood. White-blood cells, 20,000 to 600 (estimated from smears).

Differential count showed constantly 85 to 95 per cent. lymphocytes with a variable number of large pathological forms, except during a period of about two weeks following transfusion when the blood picture became practically normal.

The blood picture was characterized almost throughout by a low count and by a high mononucleosis; there was a terminal extreme leukopenia.

CASE VI.—*A case in which the blood presented a pronounced lymphemia, regarded as infectious, but not as a true leukemic picture.*

P., aged thirty-two years. Johns Hopkins Hospital.

Clinical. Fever; purpuric eruption; marked enlargement of spleen.

Blood.

White-blood cells	10,000
Polymorphonuclear neutrophiles	24.0 per cent.
Polymorphonuclear eosinophiles	1.0 "
Polymorphonuclear basophiles	0.0 "
Lymphocytes, large 60.4a Lymphocytes, small 10.0a	70.4 "
Large mononuclears	3.3 "
Transitionals	1.3 "

The blood picture at first suggests that of lymphadenoid leukemia of the large cell type; whether we have to deal in reality, here, with an infectious (non-leukemic) lymphocytosis, or with a true leukemia is not yet certain.

CASE VII.—*A case of acute myeloid leukemia in an infant.*

L. F., female, aged nine months, a patient of Dr. J. H. M. Knox.

Clinical. Fever; diarrhea; rapid anemia. No enlargement of the lymph glands or of the spleen.

Duration. Death three and one-half weeks after the onset of the acute symptoms; the diagnosis was made twelve days before death.

Blood.

White-blood cells	200,000
Polymorphonuclear neutrophiles	48.0 per cent.
Polymorphonuclear eosinophiles	4.2 "
Polymorphonuclear basophiles	0.0 "
Lymphocytes	30.8 "
Large mononuclears	0.0 "
Transitionals	0.0 "
Neutrophilic myelocytes	18.0 "
Eosinophilic myelocytes	1.6 "
B. myelocytes	0.2 "
Myeloblasts	0.4 "

The blood resembles that of chronic myeloid leukemia except in the presence of a high percentage of lymphocytes, which is probably due to the age of the patient.

CASE VIII.—*A case of acute myeloid leukemia in an adult.*

S. H., male, aged forty years. Johns Hopkins Hospital.

Clinical. Onset sudden; septic temperature; rapidly developing anemia; exophthalmos; stomatitis. No enlargement of the lymph glands or of the spleen.

Duration. Death one month after onset of symptoms. Diagnosis twelve days before death.

Blood.

Red-blood cells	970,000
White-blood cells	35,000
Hemoglobin	40.0 per cent.
Polymorphonuclear neutrophiles	21.0 "
Polymorphonuclear eosinophiles	0.8 "
Polymorphonuclear basophiles	0.0 "
Large mononuclears	5.0 "
Lymphocytes	2.0 "
Neutrophilic myelocytes	52.0 "
Eosinophilic myelocytes	6.0 "
Myeloblasts	14.0 "

The blood is similar to that of chronic myeloid leukemia, except for the high percentage of myeloblasts in association with a relatively low count.

CASE IX.—*A case of acute myeloid leukemia, the white corpuscles becoming ever more immature as death was approached.*

J. B. T., male, aged forty-seven years. Johns Hopkins Hospital.

Clinical. Sudden onset; septic temperature; rapidly developing anemia; otitis media; ulcerative stomatitis; hemorrhagic diathesis; liver and spleen enlarged; no enlargement of the lymph glands.

Duration. Death two and one-half months after onset of symptoms. Diagnosis two and one-half months before death.

Blood.

Red-blood cells	4,000,000–1,900,000
White-blood cells	17,000–280,000
Hemoglobin	72–25 per cent.

	Early.	Late.
Polymorphonuclear neutrophiles	59.6 per cent.	25.7 per cent.
Polymorphonuclear eosinophiles	0.0 "	0.3 "
Polymorphonuclear basophiles	0.0 "	0.0 "
Lymphocytes	10.6 "	6.7 "
Large mononuclears	5.6 "	14.0 "
Transitionals	1.4 "	4.3 "
Neutrophilic myelocytes	20.2 "	25.0 "
B. myelocytes	0.6 "	0.8 "
Myeloblasts	2.0 "	23.2 "

The blood picture early suggested chronic myeloid leukemia. Later it developed into that of the typical acute myeloid type.

CASE X.—*A case of acute myeloid leukemia of the chloromatous type.*

E. P., male, aged seventeen years, a patient of Dr. T. R. Boggs.

Clinical. Symptoms of acute infection; swollen eye; otitis media; moderate enlargement of the lymph glands and of the spleen; rapidly developing anemia; septic temperature.

Duration. Death three and one-half months after onset of symptoms. Diagnosis seven weeks before death.

Blood.

Red-blood cells	1,900,000
White-blood cells	184,000
Hemoglobin	40.0 per cent.
Polymorphonuclear neutrophiles	3.4 "
Polymorphonuclear eosinophiles	0.0 "
Polymorphonuclear basophiles	0.2 "
Lymphocytes	3.8 "
Large mononuclears	0.2 "
Transitionals	0.4 "
Neutrophilic myelocytes	6.2 "
B. myelocytes	1.6 "
Myeloblasts, small	34.0 "
Myeloblasts, medium	46.0 "
Myeloblasts, large	4.2 "

Unusual myeloblastic blood. The blood picture at first sight resembles that of acute lymphadenoid leukemia.

CASE XI.—*A case of acute myeloid leukemia with many unripe marrow cells in the blood.*

J. H. S., male, aged thirty-one years. Johns Hopkins Hospital.

Clinical. Septic temperature; hemorrhagic diathesis; rapidly developing anemia; no glandular enlargement.

Duration. Death three and one-half months after onset of symptoms. Diagnosis five weeks before death.

Blood.

Red-blood cells	1,200,000
White-blood cells	6700–15,400
Hemoglobin	28.0 per cent.
Polymorphonuclear neutrophiles	17.0 "
Polymorphonuclear eosinophiles	0.0 "
Polymorphonuclear basophiles	0.0 "
Lymphocytes	6.0 "
Large mononuclears	4.2 "
Transitionals	0.0 "
Neutrophilic myelocytes	3.6 "
Myeloblasts	69.2 "

The blood on cursory examination might easily be mistaken for that of an acute lymphadenoid leukemia. The cells classed as myeloblasts closely resemble the cells described by Pappenheim as lymphoidocytes.

CASE XII.—*A case of acute leukemia with severe anemia.*

B. G., male, aged twenty-six years, a patient of Drs. Leopold and Sexton.

Clinical. Sudden onset; rapidly developing anemia; coma; no glandular enlargement; spleen moderately enlarged; septic temperature.

Duration. Death twelve days after onset. Diagnosis made five days before death.

Blood.

Red-blood cells	1,100,000
White-blood cells	40,000
Hemoglobin	18.0 per cent.
Polymorphonuclear neutrophiles	31.2 "
Polymorphonuclear eosinophiles	6.8 "
Polymorphonuclear basophiles	0.0 "
Lymphocytes	51.0 "
Large mononuclears	3.2 "
Transitionals	5.4 "
Neutrophilic myelocytes	2.4 "

The blood picture is that of a marked anemia with a large number of nucleated red-blood cells, the number of these being even greater than that of the white-blood cells. The white-blood cells are young and atypical; many are fragile forms. The picture suggests that of pernicious anemia, but is in reality that of a leukemia. The term leukanemia should be avoided.

Autopsy Findings. Acute splenic tumor—splenic and hepatic infarcts—cloudy swelling of viscera.

DISCUSSION

Dr. Joseph L. Miller: What are the differential points between myeloblasts and large myelocytes?

Dr. Thomas Ordway: In the aleukemic stages, it is difficult to say that these cases are really leukemia. Differentiation between myelocytes and lymphocytes may in certain instances be decided by the oxidase reaction.

In numerous cases of myelogenous leukemia, citrated blood on standing develops a buffy coat which is yellow to apple green in color; such as may be seen in the nodules of chloroma, which some believe to be a form of leukemia in which the cells have left the blood and localized by metastasis in the tissues.

In the treatment of leukemia by radium there has been no success in the acute, fulminating type. In more chronic cases, radium acts like the x-rays but with more striking results. Most of the cases treated unsuccessfully with x-rays or benzol, when treated with radium over the spleen had marked remissions.

Dr. Frank Billings: I would like to ask Dr. Barker whether any of his cases of acute leukemia of the infectious type had actual foci of infection anywhere? I have in mind a case with an infection of the jaw, in which acute myeloid leukemia developed; also two cases of gangrenous infection of the throat followed by acute lymphoid leukemia. I recall also a case of typical Hodgkin's disease in which the glands of the neck suppurated after salvarsan therapy. The glands finally healed; the patient improved for a time and then died in an acute septic state with the blood picture of acute lymphoid leukemia.

Dr. James B. Herrick: Dr. Barker referred to what has been called acute infectious lymphemia. Is it not possible that some of these cases are really of the same character as acute lymphatic leukemia, differing only in being less virulent and in the favorable termination? May not our conception of acute lymphatic leukemia, as a disease that is of necessity fatal, be too arbitrary? I have seen two cases in which the picture was that of a subacute lymphatic leukemia including the glandular and splenic enlargements, anemia of the secondary type, fever and lymphemia (30,000); but recovery instead of the expected death occurred. In one of these instances there was the remarkable coincidence that the patient, a young physician, was caring for a perfectly typical case of malignant acute lymphatic leukemia. I believe Dr. Capps made many blood counts on these last-mentioned cases.

Dr. Alfred Stengel: Dr. Barker has very properly emphasized the difficulty of differentiating between the possible types of leukemia. I believe that many cases now called acute lymphatic leukemia will hereafter be recognized as myeloblastic forms. The digestive power found in myelocytes and myeloblasts may prove a useful differential criterion. Differentiation by selective staining is not altogether satisfactory in the case of leukemias characterized by young forms of cells.

As to the possibility of acute infectious lymphemia being recognized, large series of these cases are now being published. Cases I have seen could not be distinguished from acute lymphatic leukemia; the result alone tells the tale. All the true leukemias die despite treatment. In chronic cases *x*-rays properly used may delay the result considerably; in acute cases I have never seen it do other than injury.

Dr. S. J. Meltzer: I wish to ask Dr. Barker whether the so-called Auer bodies were looked for, in his cases of acute leukemia? I did not hear him mention these bodies. Dr. Auer described, several years ago (*Amer. Jour. of the Med. Sciences*, June, 1906), rod-shaped bodies frequently present in the cytoplasm of the large mononuclear cells. On some days these bodies were found in a large number of cells; on other days again they were totally absent. Besides the rod-shaped bodies Auer observed contracting vacuole-like bodies in the cell nucleus. A few years ago Ottenberg reëxamined old specimens of blood of several cases of acute leukemia and established in many instances the presence of the Auer bodies in the large mononuclear cells.

Dr. L. F. Barker: I had meant, had time permitted, to speak of the work of Auer, of Dock and Warthin, of Billings and Capps, and of others. Their valuable papers are often referred to in the bibliography of the subject, which is now large.

The differentiation between the myeloblast and the large lymphocyte is, sometimes, a difficult matter. Naegeli refers to the myeloblasts as an unripe, ungranulated bone-marrow cell. But, as Pappenheim has shown, there is a complex heteroplastic series of events in the development of the myeloid cells, and the differentiation between lymphocytes of lymphadenoid origin and lymphoidocytes —the youngest myeloid cells—depends largely on the recognition (1) of differences of nuclear structure and (2) of a series of transition forms (under diverse staining) between lymphoidocytes and typical myelocytes. The chemical and the enzyme reactions are also important, but it would take too long to go into their details at this time.

The treatment of these formidable acute leukemic blood states is disappointing; radium may possibly hold out some hope as Dr. Ordway

suggests. In my experience, the patients with true acute leukemia die. Cases of acute infectious lymphemia often recover. Confronted by a patient believed to be suffering from an acute leukemia, the greatest hope lies in the possibility of a mistake in diagnosis; for, now and then, infectious lymphemia is supposed by the practitioner to be acute leukemia. My associates, Drs. Baetzer and Miller, are collecting cases of this latter type, and will, I hope, soon report them. Dr. Herrick may be right in his suggestion that the infectious lymphemias that recover are in reality mild forms of acute leukemias; should it turn out so, we shall have to alter our definition of acute leukemia.

THE FATE OF FATS IN THE BLOOD STREAM*

By WILLIAM CHARLES WHITE, M.D.
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For some time I have been interested in trying to substantiate a theory, based on anatomical and chemical studies, that the prevalence of tubercles in the apices of the upper lobes of the lung in man, and in the cephalic end of the caudal lobes in cattle, is dependent upon the determination to these areas by reason of light specific gravity and directness of the current of the blood stream of certain fatty elements in the blood.

We were unable at first to secure an emulsion of sufficient fineness to answer the purpose of our experiments. During the last year we have used an ideal natural emulsion in the form of cream.

While I am unable to offer anything directly on the premise, at this time, another fact has appeared which seems worthy of report.

Rabbits were starved ten days. On the second day of starvation they were given 5 c.c. of fresh warm cream, with a specific gravity of about 1026, in the ear vein daily. They were allowed water. Their urine and stools were collected, and their blood examined daily before and after the injection of cream.

The constant blood changes were as follows, anemia, polynuclear leukocytosis, presence of fat in leukocytes and appearance of colostrum corpuscles.

After death there was found in three rabbits a very striking storage of fat in the regions supplied by those vessels coming off from the aorta in the (1) celiac axis group; (2) the renal pair; (3) the superior mesenteric group and (4) the inferior mesenteric group in this order of intensity of deposit.

* I wish to acknowledge the very helpful work of A. Marion Gammon in connection with this research.[1]

FIG. 1.—Rabbit starved for ten days, during which time 5 c.c. of cream were injected into ear veins at various intervals. Eight injections were given in all. Note deposit of fat about lymphatic vessels in mesentery, also fat deposit about spleen.

FIG. 2.—Rabbit starved for three days before death, with same previous existence as rabbit in Fig. 1.

The accompanying pictures will demonstrate this remarkable deposit around the kidneys and spleen and in the mesentery of the small bowel. The fat was also deposited in the centre of the liver

FIG. 2.

Kidneys in cream rabbit. Same as Fig. 1.

Kidneys of normal rabbit.

lobule in the mesentery of the large bowel, and half-way round the colon in the line of the mesenteric vessels. There was further a triangular deposit of fat, 3 x 3 x 0,5 c.c. in the region of the cisterna

chyli, in which all of the other deposits finally centred. This gross central deposit was likewise continuous with extensive deposits throughout the lungs. There was no subcutaneous fat.

We have long since noticed the persistence with which fat introduced into the pulmonary capillary bed by way of the ear vein and right heart is retained and persists for many days in the lung[2] and certain peculiarities in the lipase content of the lung, and have tried to find some explanation of the further fate of the retained fat.

In speaking of the matter to Dr. John J. Abel, he told me that not only had he found a corelated thing in dogs, that is, that certain particulate fats (cream) introduced into the jugular vein appeared quickly in the mesenteric lymphatics, and that he also was wondering where the transfer took place. Dr. Abel kindly referred me to an interesting reference, which he had found, to the same phenomenon in von Brüke's first volume of *Vorlesung über Physiologie*, Wien, 1875, p. 202, in an article by Herbst. I have not had time to read this carefully, but will do so for the final article.

The first impression which we had was that the transfer must come by way of the aortic blood stream after passing through the lungs. This was to my mind early eliminated as a possibility by the absence of any of the fat in the *organs* supplied by the abdominal branches of the aorta, that is, especially in the kidneys, spleen and intestinal villi.

The absence of fat in the latter completely puzzled me, and this together with the fact that we were unable to find fat in the peripheral blood stream for more than fifteen minutes after the injection, and then in very small amounts, and little fat in the stools and none in the urine, started me searching for some other way in which the injected fat could reach the places of storage in which we found it.

I was sure that in some way this transfer had to do with the lungs, and was given a lead by a paragraph in Dr. Sabin's article.[3] "For years," she says, "I have been trying to get injections of the lymphatics of the lungs and diaphragm, but never succeeded until I introduced the needle into the retroperitoneal sac." On page 55, she further adds, "that vessels from the peritoneal sac gradually extend to the bowel wall."

This led me to the suggestion that the transfer of particulate fat from the blood stream to the lymphatic vessels may be accomplished in some animals, dogs (Abel and Herbst) and rabbits (White), in the lungs. This transfer may result either by (1) ingestion of the fat by the endothelial cells of the lung capillaries and later, ejection of the fat into the lymphatic spaces around the vessels; (2) by direct passage through the intercellular spaces of the capillary wall.

From here the fat may pass backward through the lymphatic channels, thoracic duct, and cisterna chyli to the fat depots in the liver, around the abdominal organs, and along the mesenteric vessels.

This seems to me the only possible explanation of the finding in this case. If it be true that this is possible, we will need a reconstruction of our conception of the lymphatic system of the lung, its function and connection with the abdominal organs.

1. Either there is a reverse current established by hunger of the abdominal depots when there is no stream toward the subclavian vein through the thoracic duct; or

2. There may be a normal current in this direction in a separate channel accounting for the often-observed rapid disappearance of fats from the pulmonary stream.

If this be true, we must make a change also in our knowledge of the liver lymphatic system as expressed by Mall[4] in his article on "The Structural Unit of the Liver."

Mall says: "The lymphatics of the liver do not drain all portions of the liver lobule, but only those portions that are formed by the centres of the portal units. There are no lymphatics at the centre of the lobules, nor at the nodal points. At the centre of the portal units there is a very free communication between the blood capillaries and the lymphatic radicals in the tips of the capsule of Glisson. So the lymphatic circulation is marked at this point, that is, in the centre of the portal structural unit, while in the rest of the unit it is insignificant or wanting altogether."

It seems possible from our study that there may be a separate lymphatic system in the liver, having specially to do with fats, occupying the region in which Mall could find no such structures,

and connected with the cisterna chyli, the lung lymphatics and the depots of fat in the abdomen.

I have presented this subject to Dr. Florence Sabin, who kindly introduced me to her student, Dr. R. S. Cunningham, who has spent the last year working on the lymphatic system of the lungs.

The lymphatics of the lung have never been understood until this admirable work of Dr. Cunningham, which unfortunately is as yet unpublished.

Dr. Cunningham tells me that from their study of the lymphatics of the lung not only is there no surprise in what I have found, but that it is the natural and expected result of such an experiment.

The suggestion of a separate vascular system having to do with fat transfers is not a more disturbing one than the change produced in our thought by the separation of the lymphatic system from the tissue spaces suggested by the president, Dr. Meltzer.[5]

On the other hand, if it can be established that, for instance, the substances passing from the thoracic duct into the right heart, and thence to the lungs, pass over into the lymphatics in the lungs and from these back through the bronchial lymphatic glands to the right heart and so to the lungs again, and under extraordinary or normal conditions may pass from the lungs through a lymphatic system to the central portion of the liver lobule or to the mesenteric and other abdominal fat depots, many of our difficulties in understanding fat deposition and transfer in the body will be made clearer.

I hope to report more fully on this subject at a later time.

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SPONTANEOUS (NON-TUBERCULOUS) PNEUMOTHORAX

By ELSWORTH S. SMITH and J. J. BARRY
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Pneumothorax, or air in the pleural sac, is a disease that was in a way known to Hippocrates, as evidenced by the allusions in his writings to the succussion sound, and though this ancient physician did not in reality have a clear conception of the affection, he nevertheless wrote: "Among patients affected with empyema those who produce most sound when shaken by the shoulders have less pus in the chest than those who yield less sound and who are more flushed and breathless; in respect to those who do not yield any sound, but who have rales, lividity and a great dyspnea, they are full of pus and their case is desperate." Had he pursued reasoning such as this a little further he would have discovered that the real cause of the succussion was the presence of air in the pleura with the pus.

Later on cases were reported from time to time of the traumatic variety, but not until 1803 was it shown by Itard,[1] in his dissertation on pneumothorax, that the condition could be produced by other causes than external violence, and he especially called attention to the cases arising from tuberculous lesions in the lungs. But it remained for the immortal Laennec, in 1819, to first clearly present the subject in all its bearings, and his masterly descriptions

[1] Dissertation sur le Pneumothorax, etc., Thèse de Paris, 1803.

and observations, especially concerning the physical signs of the affection, remain as absolute truths today. In fact in perusing this chapter in the third edition of his work, published in 1830, one can hardly realize that he is not reading an article by some modern authority of today, so graphic, clear, and true are the pen sketches of this great French genius. He, however, had a few erroneous notions. He thought, for instance, that the air present in pneumothorax was secreted by the tissues involved, and therefore reasoned that the air coming from a tuberculous cavity was innocuous and much less liable to irritate than a body so thoroughly extraneous to the system as the air of the atmosphere, which had not been "animalized," as he expressed it, as had the air from the tuberculous cavity, for instance. This position, of course, is just the contrary of the accepted teaching of today, and yet Rosenbach and others still maintain that the pleura can transmit air just as it can absorb same, and that air may escape through the air cell and pleura simply from local lowered resistance without any definite solution of continuity. Laennec also barely alluded to the importance of the displacement of the viscera in the diagnosis of pneumothorax.

The next great contribution was that of Emerson,[1] who, in 1903, published the most exhaustive and scholarly treatise that has so far ever been written, going deeply into the theme from every stand-point, and to this masterful work we would refer anyone desiring to study the subject in all its phases.

A consideration, however, of pneumothorax in general would carry us far beyond our time limit, for, as a complication of pulmonary tuberculosis, for instance, it is, of course, a rather common condition occurring in from 2 to 14 per cent. of the cases, according to the estimation of different authors. It is, however, a very rare and fatal condition in children as evidenced by David Bovaird, Jr., being able to collect in 1903 only 18 cases from the literature of the previous ten years, including 5 of his own cases—only 4 of said 18 cases having recovered.

[1] Johns Hopkins Hospital Reports, 1903, xi.

The various causes of the disease were compiled by Biach[1] from a thirty-eight years' record of the three large Vienna hospitals. The total number of cases studied was 918 and of this number 715 were due to phthisis, and those due to unknown causes, 14. (This table is shown in detail.) So that it may be computed that about 78 per cent. of all cases of pneumothorax are caused by a tuberculous lesion, leaving about 22 per cent. of cases due to the more rare causes as pulmonary gangrene, malignant disease, etc., and out of said 22 per cent. of cases of a non-tuberculous origin, a certain, we think too small percentage, viz., 2 to 3 per cent. has been by West, for instance, considered to be of the so-called spontaneous variety. By which we mean pneumothorax developing in apparently healthy individuals without any discoverable causative lesion. That this class has appeared rather rare is shown by the studies of Fussell and Riesman[2] who, in their authoritative contribution in 1902, reported 2 such cases, and in a review of the literature from 1826 to 1902, a period of seventy-six years, were able to collect only

[1] Biachs, in 1880, collected all the cases of pneumothorax which had occurred in three hospitals in Vienna: 918 cases had been observed, which were divided according to their cause as follows:

	Cases.	Other Causes
Tuberculosis	715	Rupture of lung.
Gangrene	65	Foreign bodies.
Empyema	45	Typhoid fever
Traumatism	32	Acute articular rheumatism.
Bronchiectasis	10	Whooping cough.
Abscess of lung	10	Serous pleurisy.
Emphysema	7	Rupture of an effusion through lung.
Infarct	4	Abscess of liver.
Perforated esophagus	2	Hydatids of liver.
Abscess of bronchial glands	2	Cancer of stomach.
Ulcer of stomach	2	Perforation of intestine.
Echinococcus	1	Rupture of esophagus.
Thoracentesis	1	Tuberculosis of spine.
Worms	1	Air secreted by pleural tissue of lowered vitality.
Peritonitis	1	Putrefactive gas-producing organisms.
Fractured ribs	1	Strangulated diaphragmatic hernia infecting pleura and producing gas without perforation.
Fractured sternum	1	Total number of above stated causes 34
Uncertain	14	

This table shows that about 78 per cent. of cases of pneumothorax are tuberculous, and out of remaining 22 per cent. it has been held only 2 to 3 per cent. are of the spontaneous variety. This estimation, however, is probably too low.

[2] Amer. Jour. Med. Sci., August, 1902.

56 cases; but after a recent search of the literature since 1902, a period of only twenty-three years, we have been able to collect 145 more cases. (See tables of reported cases.) From such figures as these the natural conclusion must be that spontaneous pneumothorax is not the great rarity that it was supposed to be up to 1902, and that it probably occurs many times unrecognized.

Of the above total list of cases reported to date we should like to go a little in detail into the 3 cases it was our opportunity to observe:

Case I.—Male, German, aged twenty-five years; clerk; single. Seen July 12, 1897. Family history: Father died at forty-two years from heart failure; sick one week. No tuberculous history in family. Previous health, always good until his return to this country from Germany in 1888, when he had malaria for two or three years, characterized by irregular fever and malaise; had at this time also furunculosis. In winter of 1890–91 had coryza and nasal catarrh, with symptoms of bronchial asthma, having sneezing fits from 4 to 5.30 A.M., causing him to sit up in bed to breathe; would have some serous discharge from nose until about 11 A.M. These symptoms afterward returned, summers from 1891–94; nose cauterized in 1891. Has never had any lung trouble. Habits good.

Present trouble: On the morning of July 12, 1897, arising in his usual good health and while in the effort of buttoning his collar, was taken with a sharp, shooting pain in right axillary region, causing a feeling of "sea-sickness." Pain aggravated by every movement forced him to sit down on the side of his bed and lean forward. Toward afternoon had dyspnea on any effort, even speaking. That same evening it was possible to make out clearly the physical signs of a right-sided pneumothorax, which diagnosis was confirmed in consultation by the late Dr. G. Baumgarten. Unfortunately, at that date, we knew nothing of the *x*-rays, and were therefore denied the added evidence of the fluoroscope and skiagraph. Patient remained under observation until August 11, 1897, a period of one month, during which time, under the influence mainly of rest, the air was slowly and entirely absorbed, so that on August 15 the patient was able to go to a northern resort for two weeks. He then sailed for Europe, going to the Sanatorium at Hobenhoneff on the Rhine, where he remained about one and a half years, and where he was carefully searched for tuberculosis, with always negative results. He returned home in 1899, coming to us for another careful physical examination, which was also entirely negative. In 1906, he had what was considered a slight attack of pleurisy also on right side, lasting two weeks, from which he entirely recovered without any effusion, and remained perfectly well until May, 1897, when he had an attack of appendicitis, ending in complete recovery without operation,

since which time he has remained in the best of health. Seen on May 13, 1914, when, after careful physical examination, he was found to be perfectly well in every way: in his normal weight, that of 135 pounds, and perfectly free from any symptoms of disease.

This case must clearly belong to the class of spontaneous pneumothorax, as through all this period of time various clinicians were unable to discover any organic lesion as a basis for his attack. The case is also valuable for we have here a man apparently in perfect health eighteen years after the occurrence of the pneumothorax.

Case II.—Male, American, aged fifty years; married; physician. Family history absolutely negative as to tuberculosis. For several years he suffered from effects of hypertrophied turbinates, which condition was entirely recovered from through cauterization. No other serious illness. No previous chest trouble; all former colds were confined to his nose and throat. The history preceding the onset and of the subsequent development of the pneumothorax is especially interesting as obtained from an intelligent medical observer.

During the summer preceding, and up to within a month of the onset of the attack, patient had experienced a great deal of severe muscular strain, both in life on a ranch, when he one day broke a stirrup-strap trying to open a gate on horseback, and later on, in Arizona, at an elevation of usually over 8000 feet, in most arduous mountain climbing, and yet through all this experienced not the least respiratory distress. Returning in the autumn in what he thought was the best possible physical condition, he had, on the morning of December 4, 1910, the day of the onset of the pneumothorax, been writing about two hours on the typewriter, when he noticed a draught blowing over his feet from an open window, which was closed only after he had been in the draught for some time. After 4 P.M. he noticed severe pains, resembling the feeling in the muscles after prolonged and severe exertion, especially when associated with chilling. Pain was located along the left of the sternum, at about the second inter-costal space, and radiated across and down to the right false ribs, covering most of the anterior surface on the right side of the chest. The feeling was such that he remarked "that he had a stitch in his back, only his was in front." No other symptoms, save a trace of nasal secretion. Later pains became easier, but remained as a muscular soreness. About 6 P.M., while laughing with his friends, not loudly nor long, he felt a peculiar catch in the upper part of his trachea. He, however, then drove out in a closed cab, spending three hours at a tea, talking, laughing, and inhaling a great deal of tobacco smoke, without any discomfort in breathing. Riding home he

was able to take deep inhalations without discomfort, having first lifted up and out the back seat of an auto, tight as usual, to dust from it some snow. Thinking he had caught cold and recalling the catch in the trachea, he was surprised at the absence of substernal soreness. Slept soundly most of the night, but was disturbed two or three times by a slight dyspnea when lying on either side. Early in the morning, while walking to the

FIG. 1.—Case II of our series taken December 6, 1910, showing pneumothorax cavity; collapsed (right) lung and displacement of heart to left.

toilet, he was seized with a fit of coughing, associated with dyspnea. Cough was short, dry, but persistent, and almost exhausted him. However, he fell asleep again. A similar attack in an hour or two, on arising from bed, when dyspnea was most intense, feeling as though there was no air in the lungs and that none could get in between the short but uncontrollable coughs. He was reminded of the cough of emphysematous patients with

bronchitis. Also acute emphysema with acute dilatation of right ventricle in atheletes. No sputum at any time. Slight palpitation on arising in the early morning for a short time, but heart and pulse were regular. No cyanosis, and no tendency to go to the window, two of which were open all night. Coughing attacks, though short, were exhausting, and he was glad to lie down as soon as he could reach the bed. Leaning forward to brush his teeth, for instance, caused dyspnea, which was not experienced when he was quiet; it was a sort of feeling of suffocation.

I saw the patient about 8.30 A.M. December 5, after learning briefly the above history, and on careful physical examination was at once struck with the entire absence of respiratory murmur and of presence of distinct amphoric breathing on the right side, together with tympanitic percussion note, absence of liver dulness and extension of tympany, quite a distance to left of the median line, anteriorly. Diagnosis was at once made of pneumothorax, probably of spontaneous variety, which diagnosis was later concurred in by Drs. W. E. Fischel and A. E. Taussig. There were, however, several anomalous symptoms and signs in the case. There was no shock at any time. Pulse, 80; temperature slightly subnormal. No definite dyspnea except with effort, such as walking and coughing; only slight sensation of oppression under the sternum and a dry, irritating cough, much aggravated by speaking. No cyanosis; slight displacement of liver and heart.

December 7. Slight dulness at base, apparently changing with position of patient, quite distinct amphoric breathing, metallic tinkle and coin sound. Temperature and pulse normal; slight irritating cough; slight dyspnea.

December 9. Dulness at base of right chest the same, but as there has been no succussion sound, said dulness probably has meant return of hepatic dulness. No fever since onset. Appetite good. Very little dyspnea. Sleeps well. No pain. Ever since December 6 a quite distinct metallic tinkle has been present, and yet no succussion sound.

December 10. Amphoric breathing still distinct in right infraclavicular region. No succussion; no tinkle. General condition and appetite good.

December 13. Liver dulness today distinct at sixth interspace in right mammary line. Pulse, 88; no fever; dyspnea very slight; respiration, 24.

December 14. Since return of respiratory murmur over right apex no definite amphoric breathing. Heart about normal position.

December 17. X-ray and fluoroscope verified the diagnosis and showed no fluid. Physical signs today; liver dulness quite definite. Slight amphoric breathing and tinkle in right infracapsular region. Dyspnea and cough very slight. General condition good.

December 23. Practically no cough and no dyspnea when at rest. Liver dulness distinct. Still no succussion. Faint respiratory murmur over

apex and about root of right lung. Patient hears sounds from stomach and intestines resounded along spine as tinkling noises.

January 7, 1911. Respiratory murmur and vocal fremitus down to the level of the nipple anteriorly and angle of scapula posteriorly, which findings are confirmed by the extent of reinflation of lung, as evidenced by skiagram today. Von Pirquet and Wassermann tests were both negative.

FIG. 2.—Case II dated January 7, 1911, showing reinflation of lung and a general return to normal condition.

Patient was then sent to California for the remainder of winter, where his convalescence was uninterrupted, except that on the morning of January 20, while tying his shoe, he experienced a rubbing sensation on the right side of chest posteriorly, and Dr. Barlow, of Los Angeles, discovered a pleuritic friction which he attributed to a local edema, consequent on the complete reinflation of the lung. X-ray also showed a shadow about the

size of a dollar, at the site of the friction sound. This condition continued for about twenty-four hours and then subsided entirely. Patient returned from California early in April completely well, as evidenced by the entire reinflation of the right lung on physical examination and through the skiagram, and remains absolutely well today, five years after the onset of the attack.

FIG. 3.—Case III of our series, dated April 5, 1914, showing collapsed lung (left) with heart displaced to right of pneumothorax cavity.

CASE III.—Male, aged thirty-four years; office man. No history of tuberculosis in family. Past history: Severe bronchitis at nine months. Severe tonsillitis at nine years. Typhoid at eleven years. Subject to tonsillitis, and has the facies of adenoid disease. In his usual health when, on April 2, 1914, on arising at 7 30 A M., practising deep breathing and stretching, as was his custom, then sitting on the edge of the bed and con-

tinuing his deep breathing while putting on his shoes, inhaling at same time hot coal gas from the register, which caused him to cough several times rather hard, was just at this time suddenly seized with pain in breathing, and cough with sneezing, shooting pain in the left shoulder, which forced him to lie down propped up in bed; he broke out into a cold sweat and became very pale. He also had a "gone" feeling, as though something had

FIG. 4.—Case III dated May 7, 1914, showing reinflation of left lung with heart in normal position.

"bursted" in his chest. Pain became somewhat easier in about fifteen minutes. On seeing him at 10.15 A.M., he could not raise in bed without severe pain and rapid pulse. Physical examination: left side of thorax apparently distended; percussion note on this side markedly tympanitic, even over cardiac area. Liver dulness normal. Heart sounds quite muffled over the cardiac area and rather accentuated along the right border of the sternum. Heart displaced to right. Respiratory murmur entirely absent

over the left side, but no amphoric breathing. Diagnosis: pneumothorax probably spontaneous. Treatment, rest, and morphin for pain.

April 3. Fremitus absent on left side. Coin sound present but not amphoric breathing.

April 4. Metallic tinkle present; also metallic echo of voice, especially whispered.

April 5. Tympanitic note 2.5 cm. to right of median line of chest.

April 9. No metallic sounds today, otherwise no change in physical findings.

April 12. Amphoric whispered voice present at seventh rib and anterior axillary line. Coin sounds in fifth interspace in mammary line. No succussion. Though left side of chest has all along appeared distended, the circumference of each side has always remained at forty-three inches. No fluid in pleura.

April 15. Amphoric phenomena very slight. Some return of respiratory murmur, especially in region of root of lung.

April 17. Amphoric echo of whispered voice at angle of left scapula where heart sounds are also faintly heard at this site, having a hollow character. X-ray shows marked reinflation of lung. From this date on the progress of the case toward complete recovery was rapid and uneventful. Fever or fluid were never present. There was a gradual return of the respiratory murmur and of the heart sounds so that physical examination and *x*-ray showed on May 7 complete reinflation of lung with return of heart to its normal position and patient was discharged from hospital. During his four weeks' stay in the hospital there was a gain of five pounds in weight. Patient is now at his work again and expresses himself as being in better health than before the onset of his illness. This last case, of course, is rather recent, in which to exclude any serious organic disease, although there is nothing in the history, physical findings, of course, of the patient's ailment to suggest any definite coarse lesion back of the condition.

As to the pathological cause of spontaneous pneumothorax, there are two opposing views:

1. Dr. Parkes Weber[1] makes the following observations, which suggest the condition being due to either ruptured simple pleural adhesion or latent tuberculous focus or emphysematous bleb. He first quotes Dr. S. West, who holds that "pneumothorax can never occur in a healthy lung, as evidenced by the pressure the lungs will bear in the postmortem room without rupture; as shown also by the severe strain of whooping-cough and parturition, producing subcutaneous emphysema, but rarely pneumothorax, and more-

[1] Transactions of the Clinical Society of London, May 11, 1900, p. 171.

over when rupture of the lung does occur from various causes it also is much oftener subpleural, mediastinal or cervical emphysema, rather than effusion of air into pleura." Weber thinks that when the condition results from a sudden strain it may be due to a tear in the visceral pleura, where same may have been tied down by an adhesion. In cases furnishing no definite history of strain he feels the cause may be either an emphysematous bleb or a small subpleural latent tuberculous lesion, for he says that postmortem studies show that many individuals may have such latent tuberculous lesions and yet manifest absolutely no symptoms. Such a tuberculous lesion may also rupture and produce no pleural effusion.

The fact that most of the cases occur before the age of thirty years rather favors the tuberculous cause, but on the other hand, the preponderance of cases among the male sex speaks for the emphysematous bleb as the causative factor.

2. Hamilton[1] favors latent tuberculous focus as cause. While on the side of the emphysematous bleb as the causative factor we have:

(*a*) Fussell and Riesman, who unreservedly take this side of the question.

(*b*) Emerson stated to the writer that he had seen in the postmortem room the rupture in the classical emphysematous bleb which had caused the condition of spontaneous pneumothorax.

(*c*) Pitt[2] reports a case dying as a result of sudden pneumothorax with hematothorax, and the postmortem revealed only an emphysematous bulla, one-half inch in size, torn open, situated near the apex of the lung, and attached to said bulla was a ruptured adhesion the source of the pneumothorax and of the hemorrhage.

(*d*) Bach reports 3 cases of chronic bronchitis and emphysema, which having developed pneumothorax and coming to autopsy showed pin-head ruptures at or near emphysematous blebs. Of course, while these cases can hardly be classed as pure spontaneous cases they nevertheless show that rupture of an emphysematous bleb may cause pneumothorax; the exciting causes being almost invariably some unusual muscular effort or strain, or even some severe nervous shock.

[1] Montreal Med. Jour., July, 1908.
[2] Transactions of the Clinical Society of London, February 9, 1900.

(*e*) Only a few days ago we had the opportunity at autopsy, on a case dying of a bronchiectatic condition of left lower lobe complicated by a septic pneumonic state of left upper lobe, to see a beautiful illustration of the development of the emphysematous bleb. In this case the right lung when removed was found to be in a tremendous state of compensatory emphysema consequent on the long-continued loss of function in its fellow, it having, in fact, attained to twice the size of the average normal lung and profusely scattered all over its visceral pleural layer were millions of minute emphysematous vesicles or blebs, which on being punctured collapsed with escape of the contained air. And why this patient with his long-continued racking and harassing cough had not developed pneumothorax was certainly a mystery. But the specimen nevertheless at least strengthened our faith in the possibility of the emphysematous bleb production in pulmonary emphysema.

VARIOUS PHYSICAL EFFORTS STATED AS CAUSATIVE IN 99 CASES OF PNEUMOTHORAX

	Cases.		Cases.
Overexertion	14	Sneezing	1
Severe cough	10	Raising window	1
Walking	7	Mowing hay	1
Dressing	5	Gymnastic exercises	1
During sleep	5	Blowing horn	1
Laughing	4	Gardening	1
Inflating chest	3	Draft exposure	1
Running	2	Playing instrument	1
Rowing	2	Rolling barrel	1
Dancing	2	Carrying pack	1
Jumping	2	Playing	1
Screaming	2	Sweeping	1
Football	2	Riveting	1
Lifting	2	Books falling against chest	1
Falling	2	Smoking	1
Stooping over	1	Walking downstairs	1
Yawning	1		
		Total number of causes	33

Showing 33 different exciting causes in the order of their frequency.

(*f*) From the exciting causes, as shown in the table, we see that in 82 out of 99 cases, or about 82 per cent., some one of the thirty-three causes in the way of various physical efforts are stated as preceding the onset of the pneumothorax—it is in fact the so constant presence of these various exciting causes which largely serves to distinguish the spontaneous from the non-spontaneous varieties

of pneumothorax, for with the exception possibly of cough in tuberculous pneumothorax, we rarely hear of the non-spontaneous pneumothorax following physical efforts.

Natarp believes that the tears in his cases are located where, according to anatomical and physiological principles, the greatest air pressure is exerted, namely, anteriorly, 15 cm. below the apex.

Wintrich-Bierman believe that rupture takes place during expiration, because, according to Donders, the greatest negative inspiratory pressure is 57 cm. of Hg, whereas the greatest positive expiratory pressure is 80 to 100 mm. and greater during cough.

We have, therefore, for the support of the position of the emphysematous bleb theory, autopsy findings in 5 different cases, while, as far as we have been able to discover, there is no record of a single case of spontaneous pneumothorax diagnosed as such clinically showing at postmortem examination a latent localized tuberculous focus as the cause.

TOTAL NUMBER OF CASES OF SPONTANEOUS PNEUMOTHORAX REPORTED FROM 1826 TO MARCH, 1915

	Cases.
Fussell and Riesman (up to 1902)	56
From 1902 to date:	
Maillart and Lasserre	52
Hall	30
Smith and Barry	20
Galliard	20
Noble	2
Rosenbach	2
West	2
Emerson	1
Hamilton	1
Pit	1
Levinson	1
McDowell	1
Boland	1
Stiller	1
Widal	2
Murdock	1
Francine and Landis	1
Bach	1
Hill	1
Bieganski	1
Landman	1
Moss	1
Trans. Amer. Ped. Soc.	1
Total (since 1902)	145
(before 1902)	56
Total to date	201

STATED MORTALITY IN 147 CASES

		Per cent.
Fussell and Riesman	1 death	= 2
Maillart and Lasserre	5 deaths	= 10
Smith and Barry	0 deaths	= 0
Bach	1 death	= 5
Total, 147 cases	7 deaths	= 5

Showing only 56 cases reported during long period of seventy-six years from 1826 to 1902. While during the shorter period of twenty-three years, from 1902 to date, 145 cases were collected, speaking for the disease being at times overlooked and therefore not so rare as heretofore considered.

Diagnosis. As the table strongly suggests that spontaneous pneumothorax has been and is still being overlooked, it is highly important to have a clear appreciation of those specific data which collectively give us the true picture of the disease, as distinguished not only from the non-spontaneous varieties of the malady, but also from other diseases simulating it and this can be best accomplished by a careful analytical study of said data furnished by the 99 tabulated cases.

But first of all we must recall the definition of the disease, viz., that spontaneous pneumothorax is a pneumothorax developing in an apparently healthy individual, in whom careful examination fails to disclose any organic disease other than the pneumothorax. Therefore there will be no history of preceding ill health. No prodromata as in tuberculosis, etc. In this connection, however, it must not be forgotten that rarely, yes exceedingly rarely, a pneumothorax may be the first manifestation of a tuberculosis as in a case seen by us in an athletic but overtrained young man, who was suddenly seized while in a physical contest with a right-sided pneumothorax and who gave at the time the impression of a possible spontaneous case. He, however, had a suspicious temperature and later developed undoubted signs of pulmonary tuberculosis to which he succumbed in a year. But this case had been absolutely without symptoms prior to the onset of the pneumothorax, beyond showing evidence of overtraining. Such a case therefore shows the importance of reserving a positive diagnosis in all these cases until the patient can be thoroughly studied and observed.

CASES OF SPONTANEOUS PNEUMOTHORAX COLLECTED SINCE 1902

Case No.. Sex, age.	Reporter, date, Publication.	Side affected.	Duration.	Cause, physical.	Symptoms and physical signs.	Treatment.	Result.
I Male, 31 years	F. Parkes Weber, Tr. Clin. Soc. London, 1900	Left	32 days	None apparent	Sudden knife-like pain; difficulty in breathing; heart displaced to right; tympanitic percussion; absence of respiration sounds; coin sound present; no succussion; splash; no effusion; metallic tinkling; pulse a little rapid during convalescence	Rest in bed	Recovery.
II Male, 25 years	Sir Hugh Beevor Tr. Clin. Soc. London, 1902–3	Left,	Not stated	Lifting shovelful of coal	Sudden sharp pain; no fever; tympany over small area near sternum over second interspace; no coin sound; had similar attack four years previous	Not stated	Recovery.
III Male, 24 years	Richard Bevan, London Lancet, 1904	Left	8½ weeks	Pile of books falling against chest	Accident occurred in afternoon; no symptoms whatever until awakening next morning, when had dyspnea on attempting to arise; no pain, but extreme distress on exertion, none while lying quiet; no fever; no effusion (left) chest distended; metallic tinkle; heart apex in fifth interspace 1 inch to right of sternum; absence of breath sounds; no tubercle bacilli	Rest in bed	Recovery.
IV Male, young	B. C. Stevens, London Lancet, April 29, 1905	Left	6 weeks	Rupture of emphysematous bleb in an asthmatic condition due to overexertion day before	Amphoric phenomena; pain dyspnea; no cyanosis; no fever; silence over left side; heart to right side	Rest in bed; sedatives; diet, alcohol	Recovery.
V Male, 21 years	John McKie, Brit. Med. Jour., 1905	Left	5 weeks	While taking his morning wash	Sharp pain which persisted, although he continued his work, school teacher, for two days; no signs or evidence of tubercle bacilli; left chest slightly fuller in front; slight dyspnea; heart impulse visible and strongly felt to right of sternum; tympany over entire left chest; metallic tinkling and coin-sound succussion on fourth day	Morphine for pain and rest in bed	Recovery; patient examined 2 years later; no trace of pneumothorax.
VI Male, 18 years	W. Clifford Nash, London Lancet, February 17, 1906	Right	About 4 weeks	Running in foot-ball game	Great dyspnea; pain; no fever; all signs of pneumothorax after fourth day	Aspiration on 9th day without benefit, also on 21st day; organs normal position on 27th day; no fluid	Recovery.
VII Female 21 years	J. C. Sale, London Lancet, 1907	Right, 11 attacks	2 weeks to 7 months	Once while brushing hair; once coming downstairs; once while walking in street	Had cough and spit up some blood for 3 weeks before first attack stopped at onset of pneumothorax; no more blood spitting during or between other attacks; no signs of tubercle bacilli six years after first attack which was in 1901	Rest in bed	Recovery.

Case No., sex, age.	Reporter, date, publication.	Side affected.	Duration.	Cause, physical.	Symptoms and physical signs.	Treatment.	Result.
VIII Male, 40 years	John G. Beardsley, New York Med. Jour., 1907	Right	5 weeks	Shouting and scream-on street in alcoholic frenzy	Fell to ground with severe pain in chest; dyspneic; right chest much larger than left; coin test present; no signs or evidence of tubercle bacilli	Not stated	Recovery.
IX Male, 30 years. Sailor perfect physical condition	John G. Beardsley, New York Med. Jour., 1907	Left	6 weeks	Rowing in a 2 mile boat race	Not stated; except effusion 1 week after attack which was tapped	Not stated	Recovery; still in navy; in perfect health.
X Male, 22 years, Architect	Hamilton, Montreal Med. Jour., July, 1908	Right	3 weeks	Developed after night's rest	Was able to sing in church choir after onset; pain in chest, but no shock or dyspnea; pulse 80; no fever; tympanitic note; amphoric breathing; coin sound; heart displaced to left; no fluid	Not stated	Recovery; no recurrence 3 years after.
XI Male, 18 years, Stenographer	Hamilton, Montreal Med. Jour., 1908	Right	5 weeks	Had run some miles several days before	Severe pain increased by cough and respiration; marked dyspnea coming on in evening; typical signs of pneumothorax; fluid present after a few days; no fever; no aspiration	Not stated	Well 18 months after.
XII Male, 41 years,	Hamilton, Montreal Med. Jour., 1908	Left	Recovery uninterrupted	No cause	Giving away of something in chest followed by dyspnea and syncope; tympanitic note with suppressed breathing over left side; no coin sound; no amphoric breathing; later fluid with faint succussion sound	Not stated	Well 6 years later.
XIII Male, 24 years, Laboratory assistant	Hamilton, Montreal Med. Jour., 1908	Left	8 weeks	No cause; developed in sleep about 2 A.M.	Pain stitch-like with cough, mucopurulent sputum dark tinged; pain subsided in a few days; signs of pneumothorax present on second day; amphoric breathing and coin sound, but no succussion; dyspnea not severe; no tubercle bacilli in sputum; pneumothorax partial; very little displacement of heart as seen by fluoroscope, though cardiac dulness was absent	Not stated	Recovery.
XIV Male, 22 years	Herbert Male, Brit. Med. Jour., 1910	Left	6 weeks	Walking rapidly	Sudden severe pain; difficulty in breathing; cough, immobility of left chest; tympanitic percussion; absence of breath sounds; metallic tinkling; heart displaced to right; no effusion; temperature never above 99°; no evidence of tubercle bacilli; no tubercle bacilli in family history	Rest in bed with firm bandage around chest	Recovery.

Case No., sex, age.	Reporter, date publication.	Side affected.	Duration.	Physical cause.	Symptoms and physical signs.	Treatment.	Result.
XV Male, 36 years, Physician	O. H. Perry Pepper, Amer. Jour. Med. Sci., 1911	Right	About 6 weeks	Rupture, superficial; air vesicle during paroxysm of coughing	Insidious onset; grip; bronchitis for a few days; examination showed partial pneumothorax which became complete in next 24 hours; heart displaced some to left; tympany; amphoric breathing; coin sound; moderate effusion in few days; succussion; temperature normal; no dyspnea; no pain	Rest in bed	Recovery.
XVI Male, 29 years	O. H. Perry Pepper, Amer. Jour. Med. Sci., 1911	Left	About 2 months	Occurred suddenly while smoking a cigar, first tobacco he had used since a boy	Sharp shooting pain for a second, then comfortable until next day when sharp pain lasting an hour; dyspnea; all signs of complete pneumothorax; heart dulness 1½ inches to right of sternum; temperature normal	Not stated	Recovery.
XVII Male, 32 years	G. Morris Golden, Hahnnemann Monthly, 1911	Left	3 weeks	Sudden sharp pain, no cause stated; apparently in perfect health; no evidence of tubercle bacilli, but was assumed to be tuberculous	Dyspnea; cold, clammy; cyanosis; fever; pain; heart displaced to right; some effusion; succussion; splash; tympany; amphoric breathing; no coin sound; no metallic tinkling	Not stated	Recovery.
XVIII Male, 25 years	Elsworth Smith	Right	4 weeks	Dressing; buttoning collar button	Pain; faintness; typical signs of right pneumothorax.	Rest; cough and pain controlled by anodynes	Well 18 years after.
XIX Male, 50 years	Elsworth Smith	Right	4 weeks	Exposure to draft; laughing	Severe cough; dyspnea; gradual onset; no fever; absence of respiratory murmur; tympany extending to left of median line; heart displaced; later: amphoric breathing; coin sound; metallic tinkle	Rest; anodynes for cough	Well 3 years after.
XX Male, 34 years	Elsworth Smith	Left	5 weeks	Inflating chest; stooping to put on shoes	Pain; cough; dyspnea; shock; tympany; heart sounds muffled to left; more marked at right border of sternum; absence of respiratory murmur; later: coin sound; metallic tinkle; metallic voice; no amphoric breathing	Rest; anodynes for cough	Recovery.
XXI Female, 41 years	Hugo Bach	Right	6 weeks	Mowing hay	Pain; inclination to cough; dyspnea; slight cyanosis; anxiety; tympany; liver displaced (x-ray); whistling note on inspiration; slight exudate; no tubercle bacilli	Rest	Recovery.
XXII Male, 40 years	Charles P. Emerson, Johns Hopkins Hospital reports, 1903	Left	15 years	Running 100 yard race	Pain; dyspnea; vocal fremitus dimished; tympany; coin sound; metallic tinkle; diminished respiratory murmur; no amphoric breathing; no succussion; heart displaced	Rest	Not stated.
XXIII Male, 30 years	McDowell (Emerson), 1903	Left	3 weeks	Laughing	.....	.....	Recovery.

Case No., sex, age.	Reporter, date publication.	Side affected.	Duration.	Physical cause.	Symptoms and physical signs.	Treatment.	Result.
XXIV Male, 19½ years	Levison (Emerson) 1903	Right	3 weeks	Laughing	.....	.....	Recovery.
XXV Male, age not stated	Francine and Landis (Bach)	Right	Short time	Sudden onset while eating	Slight cough; no fever; effusion; no tubercle bacilli	.....	Recovery.
XXVI Male. Age not stated	Widal (Bach)	....	Short time	Blowing horn	Purulent effusion	.....	Death.
XXVII Male, 24 years	Hill (Bach)	Left	3 months	.....	.....	.....	Recovery.
XXVIII Male, 40 years	Bieganski (Bach)	Left	Several weeks	While sitting quietly	.....	.....	Recovery.
XXIX Male, 26 years	Landman (Bach)	Left	5 weeks	.....	No fever; effusion	.....	Recovery.
XXX	Moss (Bach)	Right	....	After a fall			
XXXI Male, 15 years	Rosenbach (Bach)	Left	4 days	Exercising on parallel bars	.....	.....	Recovery.
XXXII	Rosenbach (Bach)	....	....	Severe jar to body			
XXXIII Male, 2 years	Trans. Amer. Ped. Soc., xix, p. 183, (Bach)	....	....	.....	.....	.....	Recovery.
XXXIV Male, 22 years	West (Bach)	2 attacks, side not stated	....	.....	.....	.....	Recovery.
XXXV Male, 21 years	West (Bach)	2 attacks. right and left	....	.....	.....	.....	Recovery.
XXXVI Male	Boland (Emerson), 1903	....	....	Yawning			
XXXVII	Stiller (Emerson), 1903	....	....	Sneezing			
XXXVIII	Murdock (Emerson) 1903	....	....	Coughing			
XXXIX Male	Noble (Emerson) 1903	....	....	Overexertion			
XL	Noble (Emerson) 1903	....	....	During sleep			

Tabulation by Smith and Barry of cases of spontaneous pneumothorax from 1902 to date where data were obtainable.

Then, too, it is important to appreciate that in the vast majority of cases not only is the individual attacked while apparently perfectly well, but he is suddenly seized, dropping in his tracks, as a rule shocked by the knockout blow incident to the sudden change in intrapleural pressure. The only exception to this rule being those cases in which the rupture in the lung is so small that the escape of air in the pleura may be very slow under which conditions the onset may be gradual as in Case II of our series, but such cases are extremely rare, sudden onset being the rule. In an interesting paper, O. H. Perry Peper,[1] under title of the insidious onset of pneumothorax, goes into this phase of the subject fully, concluding that the onset was insidious in 23 per cent. of a group of 500 cases studied.

Now it is highly important to have it understood that an apparently healthy individual may therefore be suddenly seized with a spontaneous pneumothorax for it was with some difficulty that we were, on one occasion, able to persuade two most able clinicians that the patient could possibly be suffering from pneumothorax, because there was nothing in his previous record that spoke for any of the underlying causes of this disease, and only after reciting previous cases of the spontaneous variety of the malady were they finally ready to concur in the diagnosis. So that we must first fully realize that there is the well-defined affection, spontaneous pneumothorax.

Now, taking up the several tabulations of the 99 cases in order:

Table II. This forces on us the very significant fact that in at least 82 per cent. of the cases some kind of physical effort has preceded the attack. A fact that greatly assists in not only in distinguishing the spontaneous from the non-spontaneous varieties of the malady, but also from other diseases which may simulate it, for in none of these, save perhaps the cough in pulmonary tuberculosis, have we such a definite relation of physical effort as a causative factor. This table also presents thirty-two different kinds of physical efforts in the order of the frequency of their occurrence and therefore of their respective importance. That the disease may, however, come on in the small minority of cases without such

[1] Jour. Amer. Med. Assoc., October, 1911.

physical efforts is shown by the remaining 28 per cent. in which such efforts were not mentioned, and also in the 5 per cent. of cases in which the onset was stated as occurring during sleep.

TABLE OF 99 REPORTED CASES IN WHICH THE FOLLOWING DATA ARE MENTIONED

	Cases.
Duration—1 week	11
2 weeks	2
3 weeks	11
4 weeks	16
5 weeks	7
6 weeks	10
7 weeks	4
8 weeks	15
12 weeks	4
7 months	1
9 years	1
15 years	1
Age—First decade	2
Second decade	19
Third decade	39
Fourth decade	17
Fifth decade	5
Sixth decade	2
Seventh decade	1
Males	78
Females	10
Right side affected	40
Left side affected	44
Sex not mentioned	11
Age not mentioned	14
Side not mentioned	15
Duration not mentioned	16
Cases having more than one attack—11 attacks	1
4 attacks	1
3 attacks	1
2 attacks	6

Age, sex, etc., showing the preponderance of cases in the young male adult.

This table makes apparent two very important facts: First, that the vast majority of cases occur in the third, second and fourth decades in the order of their respective frequency—in other words, in young adults. While the sex incidence gives 78 per cent. male and only 10 per cent. females, from which we may conclude that the disease occurs with by far the greatest frequency in young male adults.

In this table we have, first, the symptoms in the order of their respective frequency, viz., pain, 59 per cent.; dyspnea, 52 per cent.; cough, 11 per cent.; faintness, 5 per cent.; anxiety, 2 per cent., etc.

Pain, dyspnea, and cough are therefore the most important symptoms. Faintness and anxiety, taken together, may be considered to represent shock, which figure at 7 per cent., we feel would be rather too low; for shock of more or less marked degree is a rather constant factor in those cases developing suddenly and should therefore be placed more on a par with pain and dyspnea.

SYMPTOMS AND PHYSICAL SIGNS STATED IN 99 CASES

Symptoms

	Cases.		Cases.
Pain, present in	59	Anxiety, present in	2
Dyspnea, present in	52	Oppression, present in	1
Cough, present in	11	Dizziness, present in	1
Faintness, present in	5	No cough, present in	1

Physical Signs

	Cases.		Cases.
Tympany, present in	36	Position of heart normal, present in	3
Displaced viscera, present in	28	No movement of side, present in	2
Amphoric breathing, present in	23	Slight dulness, present in	2
Metallic tinkling	22	No heart dulness, present in	2
No respiratory murmur, present in	21	Pallor, present in	2
Coin sound, present in	13	No vocal resonance, present in	1
Effusion, present in	10	Metallic voice sounds, present in	1
Distended side, present in	7	Fremitus present in	1
Cyanosis, present in	6	Shock, present in	1
No fever, present in	6	Muffled heart sounds, present in	1
No Fremitus, present in	5	Unconsciousness, present in	1
Succussion, present in	4	Hemoptysis, present in	1
Slight fever, present in	4		

Symptoms and physical signs, giving their importance in the order of their occurrence. Succussion a rare sign in this affection. Metallic tinkling present in this group without pleural effusion.

2. The physical signs also in the order of their relative frequency, viz., tympanitic percussion, 36 per cent.; displaced viscera, 28 per cent.; amphoric breathing, 23 per cent.; metallic tinkling, 22 per cent.; absent respiratory murmur, 21 per cent.; coin sound, 13 per cent. We would note here first: that absence of respiratory murmur is probably one of the most constant signs for the reason that the lung in this affection being rarely held down by adhesions, the collapse of the organ is complete and therefore the conditions are no longer present for the production of the respiratory murmur, and therefore absence of respiratory murmur as a physical sign should at least be classified with pain and dyspnea. And for the

same reason absence of the vocal fremitus should have also a higher percentage ranking in fact close, if not next, to absent respiratory murmur.

Liquid effusion was present in only 10 per cent. of the cases and succussion therefore in only 4 per cent., valuable facts in distinguishing the spontaneous from the non-spontaneous varieties of the disease, as in the latter effusion is the rule and succussion therefore one of the most important physical signs.

It is to be noted, too, that in spite of fluid being present in only 10 per cent. of the cases, metallic tinkling was found in 22 per cent., showing that contrary to the older view, pleural effusion is not necessary for the production of metallic tinkling. That the heart was not displaced in 3 per cent. of the cases should also be noted. Also that slight dulness was present in 2 per cent. This, of course, could be so without presence of fluid due to a peculiar degree of tension in the pleural air. And should the dulness in such a case be found marked, same may be misleading in the differentiation between air and fluid in the pleural sac and the aspirator may be required in the decision.

We have made these comments on the individual values of the various data in our tables for the reason that certain errors may creep into these as in other statistical studies in various ways. As, for instance, the authors reporting the cases may fail to look for or to report a certain sign. And then we ourselves may have committed occasional errors in our collection of the statistical data. With the exception, however, of the points commented upon and in the main we believe the data of our tables may be accepted as correct.

And last, but by no means least, we have the fluoroscope and skiagram which both give us a clear picture of the collapsed lung on affected side, surrounded by a large air chamber filling the involved pleural sac. They also show us beautifully the displaced organs.

Differential Diagnosis. 1. The spontaneous is to be distinguished from the non-spontaneous form of the malady. Here the results of physical and *x*-ray examinations may be identical with the exception that in the former the presence of pleuritic effusion and

its resulting physical findings are quite the exception, while in the latter it is rather the rule.

The anamnesis also in the spontaneous variety is, as a rule, negative, the subject being practically always healthy, and usually a young male adult who is suddenly seized with intense dyspnea and

FIG. 5.—Photograph of case of diaphragmatic hernia after ingestion of bismuth (recumbent position), showing abdominal viscera in left pleural cavity, compressing lung and displacing contents of mediastinum far to the right and of left dome of diaphragm downward.

shock. While none of the foregoing conditions pertain to the non-spontaneous varieties, where we usually have the symptoms of some malady antedating the pneumothorax onset, as tuberculosis, malignancy, etc., so that the subject is not healthy and is not necessarily

either a young male adult and shows physical signs of disease other than the pneumothorax.

2. Spontaneous pneumothorax must be distinguished from other conditions where, while pneumothorax is not present, the symptoms and physical findings may nevertheless simulate the condition of pneumothorax, as:

(*a*) Large tuberculous cavity, which we can, of course, at once exclude through the marked symptoms and signs of advanced tuberculosis.

(*b*) Pleurisy with effusion with amphoric phenomena at apex of lung. Here, according to Walter James[1] the signs are limited to apex. Metallic tinkle is absent, use of exploring middle may have to be resorted to.

(*c*) Pneumonia of upper lobe, generally right, with metallic percussion note and cavernous breathing—here too, as Walter James states, we have absent metallic tinkle with persistance of fremitus and the absence of true amphoric breathing, together with history and symptoms of pneumonia.

Subphrenic pyopneumothorax, this condition which resembles ordinary pyopneumothorax, even to the amphoric percussion note, amphoric breathing, metallic tinkle and succussion splash, cannot well simulate the spontaneous form of this malady because mainly of the symptoms pointing to the presence of a purulent accumulation which, of course, never obtains in the spontaneous variety of disease, but in a general way it is to be distinguished by the presence of abdominal and the absence of chest symptoms.

(*d*) Cirrhosis[2] of left lung with stomach and diaphragm high up may give tympany in lower left chest with amphoric sounds, and at times stomach succussion; but such sounds are: (1) little influenced by respiration; (2) percussion with full stomach gives dulness, and also heart is displaced to left instead of to right as it should be in a left-sided pneumothorax.

(*e*) Newton first pointed out that partial compression of a bronchus might lead to an overdistention of the lung with physical

[1] Osler's Modern Medicine, iii, 887.
[2] J. C. Wilson, Medical Diagnosis, 1909.

signs very suggestive of pneumothorax. Walsham[1] reports 2 cases from his collection of skiagrams of aneurysms in which this confusion occurred. By the use of the *x*-rays, however, the mistake

FIG. 6.—Photograph after operation. Anteroposterior view. Showing reinflation of lung with return of mediastinal contents and diaphragm to normal positions.

may be avoided by noticing the absence of the shadow which a collapsed lung gives and the increased clearness of the inner intercostal spaces.

(*f*) Diaphragmatic hernia: In 1911 we had such a case in our service at the Mullanphy Hospital in which the correct diagnosis

[1] Lancet, July 22, 1911.

was made by my first assistant, Huelsman[1] before operation, and yet two or three good clinicians differed with us, maintaining the case to be one of hydropneumothorax. We quote from the report of this case the differential diagnostic points:

"The history of injury in our case and the regularity of pain occurring on arising in the morning, uninfluenced by eating, disappearing after patient was up for a while, after intestines had returned into the abdomen. Prominence of affected side of chest Sinking in of abdomen, especially at upper portion, and perhaps what are the most important physical signs: intestinal noises in chest, together with changeable character of signs in change of position of patient, or even with patient in same position; absence of succussion splash, amphoric breathing, and of greater constancy of physical signs." All the preceding symptoms and physical signs serve to distinguish diaphragmatic hernia from hydropneumothorax, especially when combined with the evidences afforded by the *x*-rays, whereby with administration of bismuth by mouth or per rectum, some part of the gastro-enteric tube may be located within the thoracic cavity.

3. Spontaneous pneumothorax must be distinguished from those affections which simulate it in symptoms but not in physical signs as:

(*a*) Intercostal neuralgia: Case III of our series, was considered by the physician first called as one of intercostal neuralgia, but the localization of the pain along the intercostal nerves, with the tender points along the nerve trunks and the absence of all physical signs of pneumothorax, should preclude such an error. So, too, in pleurisy simple and in the diaphragmatic variety we would have the physical findings of these affections and absence of the physical findings of pneumothorax.

(*b*) Angina pectoris: Where while the pain, shock and dyspnea may be suggestive, still we would have the evidence in such an affection of preceding and present cardiovascular disease, the subject would probably be past middle life, the character, too, of the pain radiating from the precordia into the extremities, sense of impending death, etc., all of which should, taken collectively, distinguish

[1] Interstate Med. Jour., 1912, vol. xix, No. 4.

this affection, especially when confirmed by the entire absence of any evidence in the physical signs even suggestive of pneumothorax.

(*c*) The various forms of abdominal colic may in their sudden onset with agonizing pain, shock, and dyspnea at first be confusing. While there can be no question that often lesions in the thoracic cavity may for a while simulate closely abdominal conditions, when for instance, as we have witnessed, a developing pneumonia, may be mistaken for an appendicitis; the converse is also just as true that an abdominal affection may give the impression at first of some chest malady. And in this way, for instance, a hepatic colic with its sudden onset, shock, difficult breathing and referred chest pains, to angle of right scapula, etc., may at first be very misleading, in simulating a painful chest affection such as a spontaneous pneumothorax, but the history, the positive physical findings in the abdomen and their absence in the chest, should soon clear up the doubt. In this manner also should the differentiation be made for the exclusion of gastric and duodenal ulcer, renal and intestinal colic, etc.

(*d*) Gastric crisis of tabes where we may have some pain radiating through the chest with shock, but we would also have the history and physical findings of tabes and not those of pneumothorax.

The prognosis in uncomplicated spontaneous pneumothorax is, of course, uniformly good, unless the effusion of air be too sudden and extensive, or the patient's general resistance be not too much lowered by some extraneous factors.

The mortality in our collected group was 5 per cent.

Treatment. All 3 of the cases reported made a fairly prompt and complete recovery on simply rest and sufficient opium to control violent pain and stimulants to meet shock.

In cases of valvular or suffocative pneumothorax, aspiration should, of course, be done promptly. Fussell and Riesman recommend aspiration if the air be not absorbed in "a few days," but this rule appears to the writers as a rather too radical one. In Fussell and Riesman series, 10 cases tapped, 2 with stated relief. In our series, 1 aspiration but with no benefit. According to Renault and Bach the splinting of the lung by the air in pleura causing the pulmonary collapse, is the great factor in the healing process and should not be disturbed by aspiration except in most urgent cases,

and for this same reason cough and restlessness should be controlled by opium.

Conclusions of Fussell and Riesman in 1902:

1. Spontaneous non-tuberculous pneumothorax occurs in healthy persons. It is rare. It is most common in young men.
2. The pneumothorax is simple, *i. e.*, there is no formation of liquid.
3. There is rarely any febrile reaction, except perhaps in the very beginning.
4. There is probably a moderate amount of emphysema in the lung which is not recognized during life and is not incompatible with health.
5. Aspiration is a safe and certain means of relief and should be resorted to in severe or prolonged cases.
6. This form of pneumothorax is benign—all but one of the reported cases recovered.

Our conclusions at this date:

1. Spontaneous (non-tuberculous) pneumothorax is not as rare a disease as has been heretofore considered.
2. It is a disease that has been and is frequently overlooked because not thought to be due to any cause save some coarse pathological lesion as tuberculosis, malignant growth, etc.
3. Patients should have complete rest for a sufficiently long period of time to permit healing of the ruptured bleb at least four to six weeks.
4. Any influence which interferes with the splinting of the ruptured lung, such as great general restlelsness, harassing cough, etc., should be controlled by anodynes.
5. Aspiration should only be resorted to when death from suffocation and shock is threatened, due to a sudden extensive effusion of air into pleural sac, or secondly, when the effusion of air becomes chronic. There were only 11 cases aspirated out of the group 201, leaving 190 not aspirated.
6. The mortality in our collected group of cases was 5 per cent.

DISCUSSION

Dr. George Dock: The word spontaneous in these cases merely indicates that no underlying disease can be discovered or that sufficient traumatic causes seem lacking. The subjects do not give the usual evidences of emphysema; and if the condition were due to the rupture of an emphysematous bleb, it would seem that the pneumothorax would come on very slowly.

The physical signs are very positive if the examination is properly carried out, though some details vary, such as resonance. Patients usually recovery in about six weeks but there are curious exceptions. A recent patient failed to get well in seven months; he was then aspirated and 1600 c.c. of air withdrawn, showing only a slight excess of CO_2. The organs immediately returned to their proper positions; the symptoms disappeared, and in about a month there was a gain in weight of 17 pounds.

The importance of *x*-ray study of these cases should be emphasized, but the *x*-ray examination is neither easier nor more certain than physical examination.

Dr. M. Howard Fussell: Dr. Smith did not mention one variation in the physical signs which may make diagnosis difficult. This is illustrated by a case in which, after severe pain, absolute flatness developed over the affected area of the chest. Tapping at once changed the percussion note to tympany.

Dr. L. F. Barker: I am glad that Dr. Smith and Dr. Dock have both emphasized the importance of roentgenography and roentgenoscopy in studying these cases; by the employment of these methods of examination, we may escape many pitfalls in the realm of physical signs. The appearance of the see-saw movement of the two halves of the diaphragm on roentgenoscopy in pneumothorax should not remain unmentioned.

Dr. David Riesman: Dr. Torrey some time ago showed a case in which a pneumothorax had existed for four years without any impairment of the general health. During all that time the chest condition, as shown by the *x*-ray, had remained in *statu quo*.

Dr. Elsworth S. Smith: There may be heard metallic tinkling in some of these cases without fluid; it is usually thought that fluid must be present to give rise to this sign.

A STUDY OF THE ETIOLOGY OF CHRONIC NEPHRITIS AND OF THE EFFICIENCY OF THE PHENOL-SULPHONEPHTHALEIN TEST[1]

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AND

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SAN FRANCISCO

We have been much impressed with the frequency of chronic kidney conditions in patients admitted to the hospital for other ailments, and with the varying etiological factors which their histories suggest as possible causes for the condition.

A systematic study of all such cases for two years past has thrown some light on the questions of etiology and classification, and has led us to some conclusions as regards tests of kidney efficiency and methods of treatment. We shall present the facts as we find them and summarize our own conclusions. Further and different deductions may suggest themselves to others, but it must not be forgotten that medicine is not a mathematically accurate science, and a statistical study cannot always give full account of the reasons for classification in many cases. Doubtful cases have been thrown out or accounted for in a separate group so as not to disturb our main point unnecessarily. There were upward of 7000 admissions to the hospital in the two years of our observation, practically all males between twenty and sixty years of age.

Among them the initial urine examination showed that 594 had albumin and casts, although only 38 of them were admitted as cases of nephritis—34 with the diagnosis of chronic interstitial and 4 with the diagnosis of acute nephritis.

[1] From the records of the Southern Pacific Hospital.

It seemed wise to adopt at once certain arbitrary lines and to classify the cases accordingly. We therefore divided these 594 cases into two groups: those in whom the blood-pressure in absence of any other obvious cause was above the maximum normal while at rest in bed on ordinary hospital diet, and those in which it was normal or below.

Each group was studied in reference to entrance diagnosis, complications, age, occupation, use of alcohol and previous infection which were subdivided into:

1. Venereal.

2. Ordinary diseases of childhood, including mumps, measles, whooping cough, chicken-pox.

3. Scarlet fever, diphtheria, pneumonia, rheumatism, and tonsillitis were grouped together as the more serious infections.

4. All others were put in a separate group: typhoid, malaria, etc., and are referred to as other infections.

The cases with a blood-pressure above 180 were separated out from the cases with high blood-pressure. It was not possible to distinguish in all the high blood-pressure cases between chronic interstitial nephritis and arteriosclerotic kidney, but for the main purposes of this paper such a distinction is not necessary, and they will all be referred to as chronic interstitial nephritis.

The first table shows the cases according to this classification, the first group being those with blood-pressure above normal and the second those in which it was normal or below normal. It is obvious at once that the diagnosis of nephritis is practically always a laboratory diagnosis, that it exists as a complication undiscovered until some other condition brings the patient to the hospital. We are not arguing that it was not the primary condition or was not the cause of the respiratory or cardiovascular break that brought some of the patients to the hospital, but it certainly was not the appreciated condition that governed the patient's action in reporting to the company's physician, nor was it the tentative or admission diagnosis suspected in a large proportion of the cases in which it existed. (Charts I and II.)

The second very important thing (Charts III and IV) is that the etiological significance of infections, hard work, and alcohol bears a

CHART I—KIDNEY LESIONS WITH HIGH BLOOD-PRESSURE ON ADMISSION. EQUAL NUMBER OF CONTROLS FOR COMPARISON

	Non-nephritic control cases.	Total nephritic cases.	Age.		Occupation.					Blood-pressure.	
			Under 40.	Over 40.	Enginemen.	Trainmen.	Laborers.	Mechanics.	Sedentary.	140 to 179.	180 plus.
SURGICAL:											
Infected wounds	28	14	4	10	—	4	3	7	—	14	—
Non-infected wounds	37	23	6	17	1	1	9	7	4	19	4
Fractures	26	18	6	12	2	..	8	6	2	15	3
Appendix	19	12	6	6	..	1	7	2	2	10	2
Gastro-intestinal	16	22	3	19	1	6	5	4	5	19	3
Gall-bladder	2	5	2	3	..	..	2	2	2	5	—
Alveolar abscess	0	4	3	1	..	1	2	—	1	4	—
MEDICAL:											
Acute infections	61	28	12	16	3	2	8	8	7	24	4
Cardiovascular	9	45	5	40	7	2	10	6	18	26	19
Respiratory	41	26	3	23	1	5	8	4	8	19	7
Gastro-intestinal	16	21	6	15	0	3	13	2	3	15	6
Nervous and mental	13	21	4	17	1	3	10	1	1	14	7
Genito-urinary	32	17	2	15	3	1	7	5	1	16	1
Nephritis	0	34	9	25	3	4	7	8	12	15	18
Other conditions	36	46	11	35	7	2	29	9	7	36	8
Unrecorded	..	..	..	..	..	..	..	..	..	3	below normal
Totals	336	336	82	254	29	35	128	74	73	254	82
Normal controls	336		226	110	23	41	128	65	79		

CHART II—KIDNEY LESIONS WITH NORMAL BLOOD-PRESSURE ON ADMISSION. EQUAL NUMBER OF CONTROLS

	Non-nephritic control cases.	Total nephritic cases.	Age.		Occupation.				
			Under 40.	Over 40	Enginemen.	Trainmen.	Laborers.	Mechanics.	Sedentary.
SURGICAL:									
Infected wounds	26	17	..	..	..	..	..	..	..
Non-infected wounds	33	8	..	..	..	..	..	..	..
Fractures	12	16	..	..	..	..	..	..	..
Appendix	17	12	..	..	..	..	..	..	..
Gastro-intestinal	14	6	..	..	..	..	..	..	..
Gall-bladder	2	5	..	..	..	..	..	..	..
Alveolar abscess	..	10	..	..	..	..	..	..	..
MEDICAL:									
Acute infections	45	71	..	..	..	..	..	..	..
Cardiovascular	4	12	..	..	..	..	..	..	..
Respiratory	33	33	..	..	..	..	..	..	..
Gastro-intestinal	9	14	..	..	..	..	..	..	..
Nervous and mental	8	10	..	..	..	..	..	..	..
Genito-urinary	27	10	..	..	..	..	..	..	..
Nephritis	..	4	..	..	..	..	..	..	..
Other conditions	28	30	..	..	..	..	..	..	..
Unrecorded	..	..	..	..	..	..	..	..	..
Totals	...	258	173	82	13	34	95	68	54
Normal controls	258	...	179	79	20	29	95	49	65

CHART III

Possible etiological factors.	Venereal.		Alcohol.		Scarlet fever group.		Usual diseases of childhood		Other infections.		No history of any disease.		Total cases.
	Nephritic.	Normal.	Nephritic.	Normal.	Nephritic.	Normal.	Nephritic.	Normal.	Nephritic.	Normal.	Nephritic.	Normal.	
Alone	9	5	28	35	5	9	17	46	11	11	19	68	
With usual diseases of childhood	7	4	25	28	4	13	..	..	..	..	..	..	
With alcohol	4	6	..	..	4	..	..	..	..	..	..	..	
With other infections	2	1	..	6	5	1	16	23	..	..	..	..	
With scarlet fever group	2	2	..	2	..	..	..	..	..	..	..	..	
With alcohol and usual diseases	22	13	..	..	11	..	..	..	..	..	..	..	
With usual diseases and other infections	8	6	39	19	14	6	..	..	..	..	..	..	
With usual diseases and scarlet group	2	2	15	9	..	..	..	..	..	..	..	..	
With alcohol and other infections	10	6	..	..	..	..	..	..	..	..	..	..	
With scarlet group and alcohol	25	8	..	1	..	..	..	..	..	..	..	..	
With scarlet group and other infections	2	2	..	3	..	1	30	..	..	..	..	..	
Totals	93	55	107	103	43	30	63	69	11	11	19	68	336
Scarlet fever group and all other conditions	89	59											
Alcohol and all other conditions	168	136											

CHART IV

Possible etiological factors.	Venereal.		Alcohol.		Scarlet fever group.		Usual diseases of childhood.		Other infections.		No history of any disease.	
	Nephritic.	Normal.	Nephritic.	Normal.	Nephritic.	Normal.	Nephritic.	Normal.	Nephritic.	Normal.	Nephritic.	Normal.
Alone	7	3	16	24	8	8	31	37	6	9	38	45
With usual diseases of childhood	14	3	19	22	4	12	..	..	..	..	..	..
With alcohol	6	4	..	..	..	..	..	..	..	..	..	..
With other infections	2	1	8	3	..	1	14	22	..	..	..	..
With scarlet fever group	2	1	2	..	..	..	..	..	..	..	..	..
With alcohol and usual diseases	24	9	..	..	..	..	..	..	..	..	..	..
With usual diseases and other infections	6	6	..	18	4	5	..	..	..	..	..	..
With usual diseases and scarlet fever	4	1	..	5	..	..	..	..	..	..	..	..
With alcohol and other infections	8	6	..	..	..	..	..	..	..	..	..	..
With scarlet group and alcohol	12	9	..	..	..	..	..	..	..	..	..	..
With scarlet group and other infections	1	..	22	3	..	..	..	..	..	..	..	..
Totals	86	43	67	75	16	26	45	59	6	9	38	45
Scarlet fever group and all other conditions	59	46										
Alcohol and all other conditions	117	103										

very similar relation both to the group in which albumin and casts were accompanied by low blood-pressure and the group in which they were accompanied by high blood-pressure. The chief difference in the two groups lies in the fact that in the high blood-pressure cases three-fourths were over forty years of age, whereas in the normal or low blood-pressure group less than one-third were above the age of forty. In other words the incident of marked permanent structural change in the kidney bears a very distinct relation to age. This is further shown by the fact that in the control groups the age on entrance was under forty in 68 per cent. of the cases, in the group showing kidney disturbance with normal pressure 66 per cent. were under forty, while in the high pressure nephritics only 24 per cent. were under forty. Whether the normal pressure cases are on their way to early permanent change, we cannot say, but the fact that both groups show that venereal disease and infection from the scarlet fever group were nearly two times more frequent than in normal kidney cases, makes the supposition reasonable that the signs of kidney irritation in the low pressure group portend a likelihood of future kidney insult and change not evidenced by the control group.

The significance of previous infections in relation to kidney disease and kidney susceptibility can only be established by an investigation into the frequency of such infections in a similar number of cases admitted to the hospital showing no signs of kidney disturbance. If the incident of alcohol, venereal infestions, and other serious infections proves to be equally frequent and important in cases showing no signs of kidney disturbance on entrance, it is obvious that we must look further in the study of causes of kidney disease. A tabulation of 594 cases was made to show this point. (Charts III and IV.)

In Charts III and IV the kidney disturbance and nephritic cases are arranged in parallel columns with the normal controls.

Tables showing etiological factors in three groups of cases: nephritis, kidney disturbances, and controls.

Chart III. 1—336 cases of high blood-pressure, albumin, and casts in urine. 2—336 cases of normal blood-pressure and no sign of kidney lesion.

Chart IV. 3—258 cases of normal blood-pressure, albumin, and casts in urine. 4—258 cases of normal blood-pressure and no sign of kidney lesion.

It will be seen at once that certain of the infectious diseases, notably the venereal and scarlet fever groups, were from 20 to 300 per cent. commoner in the early history of chronic nephritic cases than in the non-nephritic cases. The influence of alcohol is somewhat less than might be supposed; while it was commoner as a possible etiological factor than any other condition among the nephritics, it was also the commonest factor in the control group. The fact is evident, however, that in the nephritic and non-nephritic kidney conditions, alcohol was used in from 16 to 25 per cent. more cases than in the control group. It is even important that of the cases giving no history whatever of any etiological factor there were 19 from the nephritics and 68 from the controls; 38 from the non-nephritic kidney condition in comparison with 45 from the control group.

A previous history of some diseases other than the minor children's ailments was about twice as common in the nephritics.

As indicated earlier, the frequency of venereal disease was 86 in the group of 258 with kidney disturbance, whereas only 43 among the controls had had venereal disease. The scarlet fever group was 20 per cent. larger than among the controls and the alcoholics 15 per cent. more numerous.

It seems fair to conclude that a case is made out for the definite bearing of venereal infections and the more serious infections (chiefly streptococcus and pneumococcus) as well as of alcohol on the occurrence of advanced kidney disease.

We have all understood the relation of scarlet fever to immediately consequent and uncured kidney disease. We have presumed its relation to kidney disease manifesting itself late in life even where no history of its direct consequence to the scarlet fever was shown or known.

From our results in Chart IV it certainly seems reasonable to suppose that the kidney, once the seat of trouble manifested by the presence of albumen, casts, red-blood cells, etc., in the urine,

is likely to be the seat of trouble again under conditions to which the normal kidney is more resistant.

In following the urine sediments of cases where streptococcus infection was known to exist, especially in the throat, we have been surprised to find streptococci in the urine with very little evidence of kidney disturbance, often enough to warrant us in believing that the beginning of many serious kidney disturbances is insidious, and patients are discharged cured of their primary trouble and yet harboring conditions in the urine which must inevitably lead to permanent kidney diseases. One such case in a doctor following acute streptococcus tonsillitis was accompanied by changes so slight as to have been easily overlooked had we not had this very problem under investigation, and yet three months' careful treatment by rest, milk diet and urotropin intermittently was necessary before the organisms finally disappeared.

In considering the influence of occupation (column 1) it was ascertained that the 40,000 employees of the company were grossly divided as follows. The percentage of nephritics in each group of employees and percentage in each group of an equal number of admissions from all causes are given for comparison:

	Percentage of employees in various departments.	336 admissions with nephritis. Per cent.	336 non-nephritic controls. Per cent.
Engineers and firemen	6.8	8.8	6.8
Conductors and brakemen	10.0	10.6	12.2
Laborers	40.4	36.0	38.1
Mechanics	26.4	22.3	19.4
Sedentary (office force)	16.4	22.3	23.5

Here one finds a remarkable evenness in the figures, and nothing is shown quite so conclusively as that the 16 per cent. of sedentary employees suffer more than all the others both in regard to kidney disease as well as all the other conditions requiring medical attention. Engineers and firemen were admitted with nephritis in nearly 25 per cent. greater frequency than in proportion both to the number employed and their admission for other causes. Whether the lack of exercise of the clerks and the same cause combined possibly with exposure is the cause of this condition with engineers can only be surmised.

Exhaustive work has been done to measure renal function in bilateral and unilateral disease by various urinary examinations. Cryoscopy and electrical conductivity have been studied but are not practicable. Sodium chloride and urea estimations have been carried out, especially in unilateral kidney disease. The hydrogen ion concentration of the urine has also offered a field for study and has been studied, among others, by Palmer and Henderson. The diastase test has also been used and has been favorably reported on by Wohlgemuth, von Beuzer, Heruta, Wynhausen, Marino, Rosenthal, and Geyelin.

Lactose and potassium iodide have also been employed to determine renal function but they do not appear satisfactory and the same may be said of phloridzin, which when injected subcutaneously produces a glycosuria, the degree of which is the essential end-result.

Various substances have been subcutaneously, intramuscularly, or intravenously injected to test for the rapidity and the amount of excretion based on colorimetric urinary estimations. Among these are methylene blue, rosanalin, indigocarmin, and phenolsulphonephthalein. Methylene blue has been found painful and is slowly eliminated. Rosanalin has had but a limited use and does not appear satisfactory. Indigocarmin, in the hands of a few, notably Voelker and Joseph, Baetzner, Ehrick, Roth, Tanaka, and Thomas, has given the most satisfactory results of all the kidney functionation tests. Phenolsulphonephthalein has been most exhaustively studied clinically and experimentally, and the majority of the investigators have reported most favorably as to its value. Many have made comparative studies of two or more of the above-mentioned substances. Phenolsulphonephthalein was introduced for renal functionation determinations by Rowntree and Geraghty,[1] in 1909. Among the more recent investigators of phthalein are Rowntree, Marshall, and Baetzer[2] and Geraghty,[3] who emphasize its value in nephritis and other renal disorders. Thayer and Snowden[4] states that the degree of its excretion coincided with autopsy findings. Hess[5] concluded that the phenolsulphonephthalein surpasses all other methods by its simplicity, and that it is of value prognostically as well as diagnostically. Pazzana,[6] who

studied but a small number of cases, endorses this method. Franz has satisfactorily employed this test, and recommends that the standard color solution should be made up in part of the patients' urine obtained before inoculation of the phenolsulphonephthalein. Braasch and Thomas[8] consider that fundamental surgical principles and clinical data are most important, but that the excretion test aids in differential diagnosis. It has only a limited value prognostically. Smith[9] found the test to parallel with great constancy the pathological condition of the kidneys. Intravenous administration was carried out in some cases. Siegel[10] has reported on its value diagnostically and prognostically in all types of nephritis and in surgical kidneys. Recently studies have been made, and their value emphasized, on the blood nitrogen retention in renal disorders. Frothingham[11] believes that the blood-pressure estimation, repeated routine urinary examinations, and the excretion of sodium chloride are the most reliable diagnostic methods. For diagnosis the most useful examinations are for non-protein nitrogen in the blood, to determine the ability of the kidneys to excrete extra nitrogen in the urine and phenolsulphonephthalein.

Hohlweg[12] has favorably reported on the examination of blood for residual nitrogen. Quinby and Fitz[13] have employed Prussian blue intravenously as well as indigocarmen and phenolsulphonephthalein. Urines were examined for total chlorides, nitrogen, disastase, and hydrogen ionization. They used dogs with experimentally produced unilateral nephritis. They conclude that phenolsulphonephthalein and nitrogen excretion are the most useful tests. Austin and Eisenbrey,[14] studying experimental nephritis in dogs, found that the anatomical appearance of the kidneys bore no definite relation to nitrogen, chloride, or phenolsulphonephthalein elimination. They concluded that phenolsulphonephthalein elimination seemed to be a better indicator of kidney excretion than either the anatomical changes or the elimination of total nitrogen or chlorides.

Personal Observations. Following the technic as described by Rowntree and Geraghty, 67 patients were studied with the phenolsulphonephthalein test, and 75 injections were made. It is unfortunate that many of the patients received only one injec-

tion. General medicine and surgical conditions were represented, and most of the cases showed albuminuria. Of the 67 patients, 36 (50 per cent.) were nephritics, one with acute parenchymatous, 13 with chronic parenchymatous, and 22 with chronic interstitial nephritis. Of the non-nephritic group the average excretion for two hours was 51.4 per cent. The lowest was 35 per cent. in a case of lumbosacral myalgia and no demonstrable signs of nephritis. Two cases of neurasthenia showed 35 per cent. The highest percentage was 77 in a case of cholelithiasis. The case of acute parenchymatous nephritis was a resolving one with a systolic bloodpressure of 152 mm. and a phenolsulphonephthalein output of 56 per cent.

Upon one case of chronic parenchymatous nephritis the Edebohls operation was performed. The phenolsulphonephthalein output of 10 per cent. before the operation rose afterward, with marked clinical improvement, to 32 per cent. within two weeks and to 52 per cent. three months afterward. Within six weeks therefrom, owing apparently to indiscretion in diet and under physical exercise, uremia developed. The youngest patient in this group, aged eighteen years, gave the lowest output, 14 per cent. Her condition was that of impending uremia. She left the hospital and was unfortunately lost sight of. Except one, all of the remaining cases of parenchymatous nephritis were in fair physical condition, showed an average systolic blood-pressure of 150 mm. and gave an average output of phenolsulphonephthalein of 35 to 40 per cent. One case only showed an excretion (65 per cent.) that did not parallel the severe cardiorenal condition (systolic blood-pressure, 80 mm.).

Of the cases of chronic interstitial nephritis all but one showed a parallelism of phthalein output and clinical symptoms. This case, one of hepatic cirrhosis, a few days after admission excreted only 12 per cent. After two months he had somewhat improved and the excretion was 35 per cent. The lowest percentage obtained in any case was 7.5. The patient died the following day of uremia.

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ON THE PROBABLE TOXIC EFFECTS OF PROLONGED ADMINISTRATION OF PARATHYROID GLAND

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CINCINNATI

The effects of prolonged administration of powdered parathyroid gland are so imperfectly described that the following case seems worthy of note, the more so as it possibly sheds light on the clinical manifestations of hyperactivity of the parathyroid glands.

A middle-aged married woman was referred to me more than two years ago. For a number of years she had suffered with paralysis agitans. There was nothing of importance in the family history or in the patient's past history. The present illness had begun insidiously several years ago, and various therapeutic measures had been tried without success. Some twenty months before the patient came under my care, fresh parathyroid gland of the ox was administered daily for several weeks. Then, about eighteen months before I saw her, this was discontinued and she was given Armour's powdered parathyroid gland, grain j, in capsules thrice daily. Apparently, there was improvement in the patient's symptoms for some months.

After eleven or twelve months of parathyroid administration the patient is said to have begun to fail. However, the powdered gland was continued uninterruptedly until she came under my care. The history during this time, as I have been able to obtain it, is unsatisfactory, for the patient's recollection of recent events is dim, and for a part of the time her memory is a blank. From the nurses' bedside chart, the greater part of the data is obtained. For at least three months, the patient's mental state had been abnormal. She was oriented in regard to place, but had no idea

of time. There was apparently great indifference to surroundings; she took little or no interest in what happened. She usually refused to answer questions, though there was no interference with speech or hearing. Her memory was poor. She often refused food or medicines; for a time it was necessary to conceal the medicines in the nourishment. When the patient did talk, it was often incessant for an hour or more, and usually what she said was irrational. She was frequently irritable and cross. In the night, especially, she was apt to sing for an hour or so at a time. For many months she had a purposeless habit of knocking on the wall. Auditory hallucinations were present, but no visual hallucinations were noted.

Insomnia was one of the earliest symptoms to make its appearance when the patient began to fail. It is impossible to give any definite statements previous to the time the special chart was begun. For three months the amount of sleep the patient had has been accurately recorded by the two nurses who were constantly with her. From their notes the accompanying chart has been made. From this it is evident that the patient's sleep never amounted to as much as seven hours, except the first day charted. On this occasion the patient slept only three hours during the night, but had five hours' broken sleep during the day. The longest period of uninterrupted sleep the patient had during the first two months charted was about two and a half hours. She was always very restless and wakeful.

Motor unrest was pronounced at times. The patient would toss in the bed, pitching her body and throwing arms and legs about. Because of this, it was necessary to have someone with her constantly, to prevent the patient's falling from her bed. For three months or more the patient urinated and defecated in bed. There was apparently no loss of sphincter control, as subsequent events seemed to show. Rather, the patient was quite indifferent to what happened. Her language and manner were at times coarse, quite at variance with the charming, sensitive, highly refined individual she proved to be.

Much of the time the patient had tachycardia, the pulse being between 100 and 106, weak and irregular, as recorded on her chart.

The blood-pressure was not recorded until seventeen days after discontinuing parathyroid; then, it was 120 systolic. Menstruation occurred regularly at the normal interval of time. There was rather marked anorexia.

At my first visit I found the patient lying in bed in the dorsal position. She seemed quite unconscious of those about her, and from time to time made brief comments, which evidently related to auditory hallucinations. The patient was well nourished. The color of the skin and mucous membranes was good. There was no enlargement of the lymphatic glands; the thyroid gland was not enlarged: there was no thrill or murmur over it. The pupils were equal, and reacted actively to light and accommodation. The patient refused to coöperate in attempts to test the extra-ocular muscles. The tongue was moist and clean, the teeth in fair condition.

The lungs were clear on percussion and auscultation. The heart apex was neither seen nor felt. By auscultation the sounds were loudest in about the normal position. Relative cardiac dulness was not increased. The sounds were rather weak but clear. The pulse was regular in force and rhythm, 24 to the quarter minute, rather small volume, fair tension. There was no thickening of the vessel walls.

The abdomen was about on a level with the ribs. The liver and spleen were not felt; by percussion neither was enlarged. There was apparently no tenderness on palpation and there was no rigidity. There was a small bed sore over the sacrum.

No tremor was noted in the extremities. The tonus of the muscles was distinctly increased. The biceps and triceps tendon reflexes were present. The knee-jerks were present and were not increased; the plantar reflexes were normal. There was neither patellar nor ankle clonus. The abdominal reflexes were present. Sensation could not be tested satisfactorily.

During the course of the examination the patient defecated in bed but seemed perfectly unconscious of the fact. It was soon evident, however, that the passage of urine and feces in the bed was not due to loss of sphincter control—for the patient asked for the commode at times and used it—but rather to her mental state. The urine was normal. The blood was also negative. A differential

count was made; it was normal. The record was unfortunately lost.

Within two days after my first visit, the parathyroid gland was discontinued and the patient was given tincture of nux vomica before meals, veronal and cold sheet packs at night. The second night, after discontinuing the parathyroid gland, the patient slept seven and a half hours with the aid of 7½ grains of veronal. This was the best night's sleep she had had since the bedside chart was begun three months previously. Within a week involuntary defecation ceased entirely, and after two weeks, the patient no longer voided urine in bed. The tenth day after opotherapy was stopped, the patient slept two and a half hours during the day and seven and a half hours during the night without veronal, which was then discontinued. In the two years which have elapsed since then, she has slept well and has rarely required drugs. The bed sore healed promptly.

For about two months after the parathyroid extract was stopped, the patient remained abnormal mentally, though she showed steady improvement. She was very wilful and obstinate and insisted on having her demands granted. She often exhibited childish retaliation when not allowed to have her own way.

Seventeen days after the parathyroid extract was withdrawn, the patient was wakened from sleep by a convulsion of short duration which involved chiefly the flexors of the extremities, the nurse reported. It lasted only a few seconds. A more accurate description could not be obtained. The next morning when I saw the patient, physical examination showed nothing more than previously. Thinking that the convulsion might possibly have been due to the discontinuation of the parathyroid gland, Trousseau's and Chvostek's signs were tried; each was negative. Nevertheless, the patient was put on calcium lactate and was given one grain of Armour's parathyroid gland substance every third day. There has been no recurrence of the convulsion.

The mental condition of the patient finally became normal, nearly three months after parathyroid was stopped. She said she had no recollection of events for six months, including the first two months of her convalescence. The tremor became more pro-

nounced ten days after stopping parathyroid gland substance and has remained so.

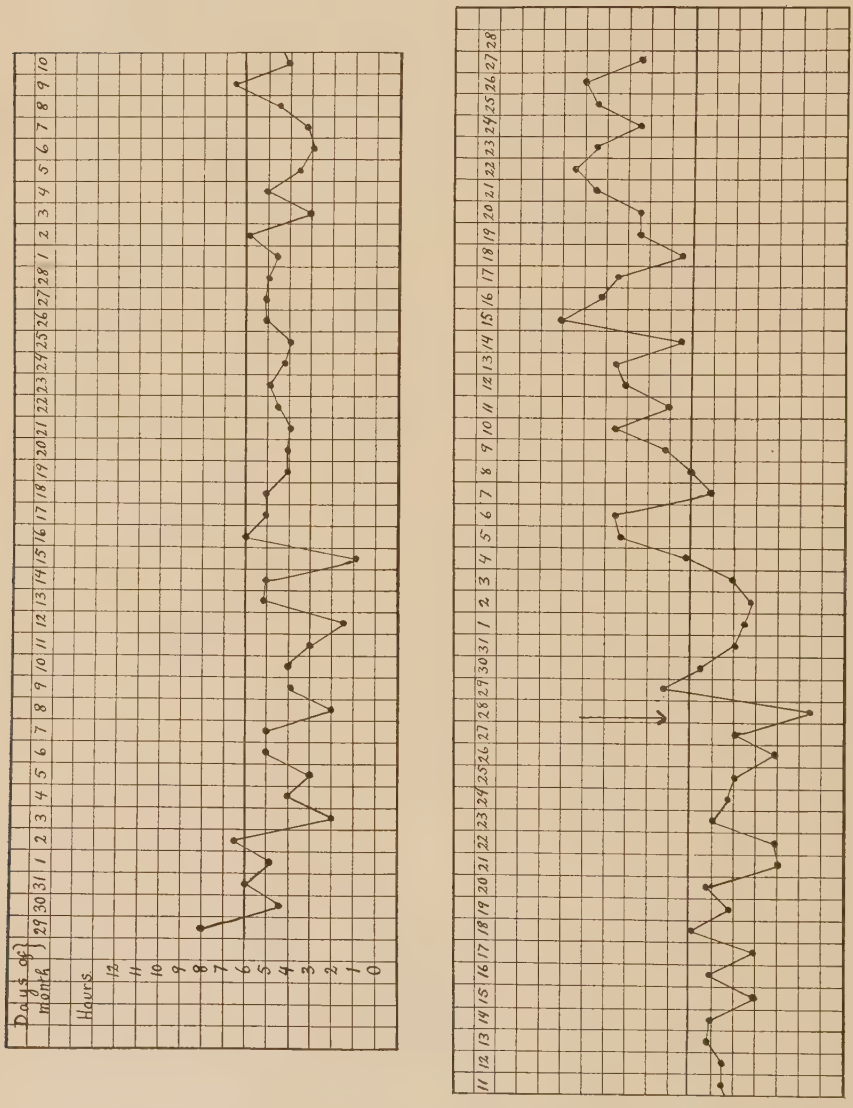

Chart showing the amount of sleep daily. The arrow indicates the day on which parathyroid administration was discontinued.

The evidence points strongly to the view that the symptoms narrated above were due to the powdered parathyroid gland,

which the patient received for eighteen months. The promptness with which recovery began after the gland was withdrawn is suggestive. Furthermore, in the text-books which I have consulted on Parkinson's disease, I have been unable to find a description of symptoms similar to those my patient suffered from; it is certainly not a usual complication of the disease.

The dosage of parathyroid gland is very indefinite. I have been able to find practically nothing in the literature. It would seem, however, that my patient received liberal quantities, for she was given one grain of the powdered parathyroid gland (Armour's) three times a day. This is so prepared that one grain of the powdered gland is equivalent to six grains of the fresh gland. When one recalls that the total weight of the four fresh parathyroid glands in man is usually 0.14 gram., according to Thompson,[1] it would seem that the equivalent of 18 grains or 1.2 gm. of *fresh* ox parathyroid per diem would be an overdose. Indeed, it seems surprising that unpleasant symptoms did not occur sooner after beginning the treatment.

A description of toxic effects from the administration of parathyroid gland, I have been unable to find in the literature. Berkley[2] refers to it very briefly in discussing the treatment of paralysis agitans with parathyroid nucleo-proteid, prepared according to Beebe's method. He says, "I have had but one or two patients out of the hundred or more in my own care who really had an idiosyncrasy for ox-parathyroid. These could not take it in any form or dose without such disagreeable by-effects, 'nervousness' and insomnia, that it was impracticable to continue the medication." Brief though it is, this would seem to have an important bearing on the case reported above, in which insomnia was so striking.

Salvioli and Carraro,[3] in an experimental study of the effect of watery extracts of ox-parathyroid gland on the circulation, reported a fall in blood-pressure following intravenous injections which was not due to local action on the vessel wall, nor was it from action on the vasomotor centre. They concluded that parathyroid extract acts as a poison on the heart muscle, whose strength it lessens. This observation may possibly throw some light on my

case. During the height of the supposed toxic symptoms, in addition to the moderate tachycardia already noted, there are frequent entries on the bedside chart describing the pulse as "weak" or as "irregular." The pulse was small and weak but I was unable to detect any irregularity, though it must be recalled that the patient received the extract less than two days after I first saw her.

As the symptoms from which the patient suffered were chiefly mental, it is impossible to reproduce the condition in experimental animals. Similar experiments in man are, of course, not to be considered. As a result, the interpretation of the case, as I have outlined it, must remain in doubt for the present, at least. It seems possible, however, that somewhat similar clinical syndromes may eventually be found to be due to overactivity of the parathyroid glands,—in other words, to hyperparathyroidism. Should such prove to be the case, it would lend support to the supposed toxic origin of the symptoms in my patient.

It is a very great pleasure to acknowledge with sincere thanks my indebtedness to Dr. W. S. Halsted of Baltimore for his generous assistance to me in searching the literature.

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CHRONIC INTERSTITIAL NEPHRITIS AND ARTERIOSCLEROSIS[1]

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No agreement has as yet been reached as to the nature of and the progressive changes leading up to the granular kidney. Almost all the factors having to do with the carrying out of the normal kidney function, as well as the known factors giving rise to processes of fibrosis in other organs, have been mentioned as the inciting cause of renal sclerosis. Particular weight has been placed upon certain of these factors because of their presence during one stage of the disease, but the opportunity of weighing their importance as an active cause for the contracted kidney has not been sufficiently good to direct a knowing finger at them. No one has yet been able to describe in a single instance the sequence of events from the beginning to the fully developed chronic interstitial nephritis. Thus opportunity has remained open for wide speculation on the interpretation of the pathological processes involved.

Some attempt has been made to link up the clinical and urinary findings with the successive changes that were taking place in the tissues of the kidney. These, however, have added little in our understanding of the process. True it is, that with the fully developed disease certain manifestations make their appearance, and we believe that some light has been thrown upon the correlation of the urinary character with the altered functional capacity due to renal sclerosis. But as for saying that the clinical manifestations bear any relation to the structural change of the kidney

[1] From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pennsylvania.

prior to the stage of granular contraction, or better, that we can forecast the outcome or even suggest the past processes in the kidney by clinical analyses, we have no definite evidence.

Thus the problem has been left in the realms of conjecture, and in the absence of incontestable proof by experiment our knowledge concerning the development of the granular kidney has not materially advanced since the days of Gull and Sutton. In the face of this we do not wish to minimize the value of the many observations which have given us a clearer understanding of some of the finer reactions in the kidney substance, but it would appear that the minutiæ of some of these observations have led us astray from the broad aspects of the problem. That Jores should find a splitting of the internal elastic lamina of the renal arterioles and from this finding discuss the importance of those still indefinite factors inducing arteriosclerosis as of prime importance for kidney disease, is, it seems to us, quite aside from the main issue.

For the main part, as was brought before this Association last year, studies upon the pathological nature of chronic interstitial nephritis have been made upon the advanced form of the disease. The criterion for the recognition of the important type of the disease is still based upon the description of the kidney as given by Richard Bright. If we adhere closely to these described characters we will find that there is a general similarity grouping them into one class. Gradually, however, our attention has been drawn to the fact that there are other forms of renal sclerosis, differing to a greater or less degree from the type here under discussion and readily recognized by careful observation and supplemented by the microscope. Thus we have kidney fibroses associated with hydronephrosis, ascending infection of ureter and bladder, hematogeneous infection (pyogenic), infarcts, thrombosis, amyloid disease, syphilis and other infective granulomata and arteriosclerosis. But when we are speaking of the small contracted or granular kidney we have in mind a diseased condition of the kidney which is different from each of these. It is different not only in the structural changes induced, but it is different also in its progress and in the distant systemic responses. The small granular kidney is recognized by its small size, the thickening of its capsule with adher-

ence to the underlying cortex. The kidney substance when stripped of its capsule is distinctly granular, each granule being surrounded by a depression from which fibrous tissue radiates parallel with the ascending vessels. The kidney substance may appear red but on the other hand, may be quite pale with not a few of its granules as yellow as the adrenal cortex. The cortex is most markedly altered and is commonly only half the thickness of the normal structure. Within it are found many fine wedge-like sclerotic areas which occupy the position between the granules observed on the surface. Alternating with these areas of fibrosis a fairly normal kidney tissue is observed. Along the patch of these radiating fibroses the tubules and Malpighian corpuscles become involved. The medulla is less altered, although a hyaline fibrosis not infrequently surrounds the excretory tubules. As in other regions subject to progressive fibrosis, a considerable adipose tissue develops in the surrounding structures, particularly about the pelvis.

At the present time, opinion as to the development of this form of the interstitial nephritis has been divided mainly between two schools. The one considers it the outcome of a low-grade but progressive inflammation, while the other believes it the result of a primary circulatory disturbance with a secondary atrophy and replacement fibrosis. Unfortunately, the issue has been somewhat confused by the further introduction of the terms primary and secondary interstitial nephritis. Each group claims that their explanation is adequate for the so-called genuine contracted kidney. We would do well to drop such irrevalent terms and leave the application of a new nomenclature to him who clearly indicates the pathological sequence of events concerned in chronic interstitial nephritis.

Gull and Sutton considered the relationship of the arteries to the diseases of the kidneys as a peculiarly intimate one in which the arterial processes preceded and determined the interstitial nephritis. No agreement was reached by subsequent workers of the actual nature of the arterial disease, some viewing it as an endarteritis (Thoma), others as an hypertrophy (Johnson, Ewald, Friedmann), while the subsequent work by Prym and Jores drew attention to the arterial lesion as a true arteriosclerosis. Jores furthermore

contended that the associated arterial changes in other organs, as was described by many, was also an arteriosclerotic process. The differentiation of this process as essentially an arteriosclerotic one and not endarteritis rested upon the finding of deep arterial degenerations associated with a splitting of the internal elastic fiber. As Jores, however, observed, arteriosclerosis may occur in the arteries of other organs in the absence of sclerosis of the renal vessels.

While the above authors were contending the dependence of chronic nephritis upon disease of the bloodvessels, Ziegler maintained the differentiation of types of chronic nephritis into groups associated or unassociated with arteriosclerosis. Those kidney lesions resulting from arteriosclerosis he believed to be individual and of a purely degenerative character and designated them the arteriosclerotic kidney.

Both Jores and his pupils repeatedly remarked that chronic interstitial nephritis is a disease most frequently encountered in advanced life, a period when arteriosclerosis is also most prevalent. Nevertheless, they remark upon the finding of occasional cases in which they have been able to demonstrate advanced renal sclerosis unaccompanied by arteriosclerosis within the kidney. This agrees with the finding of Orth, who believes that in chronic interstitial nephritis the vascular changes are not essential because their variety does not correspond with the extent of the lesions. Roth described a number of cases in which renal sclerosis was advanced but in which the arteries did not show the type of sclerosis defined by Jores as arteriosclerosis. He did, however, find that the arteries were affected by a connective tissue thickening of the intima with splitting of the elastic lamina. As, however, processes of degeneration were wanting he refused to call it arteriosclerosis. He suggests that these vessels might subsequently show arteriosclerotic change. From his observations we can only conclude that the kidney lesions have advanced with greater rapidity than those in the intima of the renal vessels and his cases illustrate the point we wish to make that the narrowly defined form of arteriosclerosis as given by Jores is not an essential factor in bringing out subsequent interstitial nephritis.

Roth described three cases of chronic interstitial nephritis without arteriosclerosis. In the kidneys, however, endarteritis was present in the smaller arteries. The cases were of relatively young individuals and all of them had definite chronic or recurrent heart and arterial disease. Yet with it all neither Jores nor his pupil sees any direct relationship inasfar as a common causative factor is concerned in the simultaneous and progressive lesions in these three organs. These authors lay much stress on the finding of a single sclerosed arteriole or the mildest beginning of intimal degeneration as indicative of the influence of arteriosclerosis upon the kidney. No recognition is given to the fact expressed in their own cases that the fibrosis of the kidney was markedly advanced and in the late stages of contraction, while the arteriosclerosis was only beginning. We can in no way follow the conclusion of this author as illustrated by his own cases that the chronic interstitial nephritis was the result of the early endarteritis demonstrated.

In the admirable work of Councilman (1897) the part played by the inflammatory process in bringing about the interstitial lesions of the cortex of the kidney was well demonstrated. In part, the cases studied included some of scarlet fever, diphtheria, pneumonia, and other infections, and the lesions described were of the nature of diffuse non-suppurative interstitial nephritis or types of glomerulonephritis. Of the latter, two forms were distinguished, a non-suppurative exudative form and a proliferative type. No clear distinction can be made between the etiological factors present in these two types and it would seem that both may arise from the same causative factor. At the time of carrying out his work bacteriological methods were not available to make a distinction between the various forms of streptococci and we find the author speaking of the organisms isolated from cases of heart disease as pneumococci. I believe we will be correct in interpreting these results as indicating the presence of the streptococcus viridans group. These organisms were found in cases of glomerulonephritis in large percentage; but the author's descriptions of the lesions indicate a transition between the glomerulonephritis and the diffuse interstitial type. The work of Wagner bears out these findings particularly in indicating the importance of the inflammatory process of scarlet

fever and other infections in bringing about permanent interstitial change.

The work of Councilman is among the few in which a study of the progressive lesions of the kidney was accompanied by bacteriological examination. Of this he says, "Various forms of disease of other organs, particularly of the heart, are often associated with them, and bacteriological investigation has frequently shown in many cases the presence of certain organisms in the kidneys. In most cases the bacteria are found in some other lesion and in the blood and their presence in the kidneys is but a part of a general septicemia. Moreover, the same conditions in the kidneys may be found associated with various organisms, and the same organisms may be associated with widely different anatomical lesions." A very fertile field awaits the routine study of the bacteriology of the kidneys in conjunction with the histological examination of all types of infection. The work which has been performed up to the present time is very suggestive of indicating the actual presence of bacteria rather than their toxins in the interstitial response of the kidney.

Undoubtedly what appears as complete disagreement in the personal observations on chronic nephritis lies mainly in the methods and material studied. Although the anatomical classification of kidney diseases has not found favor with either the clinician or the pathologist, yet in the absence of a better substitute we all revert to this method. Muller attempted an etiological classification which as yet is hardly practical and Herrick while finding the old anatomical grouping unsatisfactory offers nothing to replace it.

The types of nephritis which today attract our attention as the forerunners of the contracted kidney, are the acute glomerulonephritis and the acute non-suppurative interstitial nephritis. Without desiring to describe the various types of glomerulonephritis as well as the variety of interesting lesions that may be observed in the Malpighian body and Bowman's capsule, there is ample evidence that, in the human, these glomerulonephritides are infective lesions (Councilman, Gaskell, Baehr). The important feature lies in the fact that the glomeruli become the centres of inflammatory response in which a non-suppurative exudate and endothelial

proliferation of the capillaries or a proliferative response of the inner lining of the capsule is commonly observed. The occlusion of the capillaries of the glomerulus by cellular proliferation or by thrombosis is only an added complication; and the subsequent degeneration that occurs in the tubules of the kidney is also to be viewed as a secondary disturbance depending upon vascular change rather than an injury produced by the primary factor.

A study of these cases of glomerulonephritis soon convinces one of the varying picture, even during the acute stage. In some, thromboses of the glomeruli are common, in others rare, or the lymphocytic infiltration of the glomerulus is great and confined to this structure; others again show the inflammatory reaction diffuse, surrounding Bowman's capsule, infiltrating the stroma between the tubules and following the course of the interlobular arteries and vessels of the intermediate zone. Many such cases have been described by Councilman, Ziegler and others. In fact, the picture presented by those kidneys, in which the inflammation is more diffuse, simulates more closely the type of acute interstitial non-suppurative nephritis. This latter type which was originally discussed as a disease of the kidneys found after scarlet fever, measles and sometimes smallpox, is now being incorporated with the glomerulonephritis, mainly because a certain amount of glomerular disturbance is always present. Fahr finds the streptococcus and pneumococcus most frequently associated with acute interstitial nephritis and finds also that the same organisms are the chief cause of glomerulonephritis.

In short, although there are varieties of glomerular lesions and we encounter forms of inflammation of the kidney stroma, there does not appear to be any difference in the causative agent, most frequently the streptococcus viridans. We must, however, point out that the bacterial infection reaches the kidney under different circumstances and in a somewhat different form in the various systemic diseases in which it is met. It is because of the bacterial clusters or small infective thrombotic masses which are liberated in heart disease that give rise to a type of glomerular infarction. In this way, particular structures in the kidney are more intensely involved than others. So too, in cases of bacteriemia, by organisms

of low virulence, the kidney as well as other organs becomes a local focus of infection, and this is particularly true in the bacteriemia of acute rheumatic fever in which the heart and bloodvessels are also affected. In these infections, the heart may be involved in a variety of ways and when the endocarditis becomes well marked the kidney may be subject to embolic processes in its glomeruli so that both the acute interstitial and the glomerulonephritis are simultaneously prominent. Hence it is obvious that to state that a definite type of kidney lesion is constantly to be found as a disease associated with infection of other organs is only voicing a rule with prominent exceptions.

The frequency with which acute interstitial and glomerulonephritis are present with infective heart disease is known to all who have observed these cases at autopsy and studied the tissues. It is furthermore easy to demonstrate the fate of the early inflammatory process. Fibroses of the glomeruli, of Bowman's capsules and of the intertubular stroma may be demonstrated in all stages of formation and recurrent attacks of these infective processes give rise to combinations of inflammatory responses in the kidney tissues. The question immediately arises whether the localization of these inflammatory processes gives us definite types whereby their future scars may be recognized. In answer to this the best reference is made to a few experimental results. In these it has been shown that inflammatory reactions in the kidney due to bacterial agents are prone to follow and surround the course of the bloodvessels, particularly the interlobular vessels and the ascending cortical branches as well as the afferent arteries of the glomeruli. Associated with these inflammatory responses there are not infrequently glomerular reactions infiltrative, proliferative or thrombotic. The progress of these lesions is similar to that in the human kidney and the end result is a process of fibrosis radiating in its character with shrinking and granulation of the cortex and contraction of the entire kidney. Such lesions were reproduced in animals by the use of organisms (various members of the streptococcus viridans group) isolated from infective heart disease, and the responses in the kidney were found to be accompanied by myocarditis, at times an endocarditis and in a few cases pericarditis.

In only a few instances were systemic intimal arterial lesions obtained, although the perivascular response was always noted. Here then we have evidence of the development of the various stages of the contracted kidney in the presence of chronic infection and in the absence of primary arterial lesions.

These findings are in accord with the observations on human material and explain the occurrence of the contracted kidney in the first half of life as well as its greater frequency in the later years. Like all chronic diseases, the frequency of chronic interstitial nephritis is greatest in the late decades and it is also a rather depressing outlook when we find that the incidence of these chronic diseases shall increase with the saving of more lives in childhood from death by scarlet fever, acute rheumatic fever, chorea and other streptococcus viridans infections. We must also equally appreciate that the heart and arteries suffer, sometimes much, at other times less by invasion of these bacteria. In the arteries an endarteritis, a mesarteritis and a periarteritis have all been repeatedly demonstrated in these infections during the early years of life. Of the heart lesions, we need make no other comment than reference to Aschoff's studies upon focal myocarditis, and of the frequent presence of endocarditis in the human and in experimental infections.

What, then, is the relation of renal arteriosclerosis to chronic interstitial nephritis? Before one can answer this we must have a clear understanding of the nature and genesis of arteriosclerosis. It is not enough to boldly speak of general arteriosclerosis as of common type and constant origin. Nor is this true within the kidney itself. There are arterial lesions within the kidney whose origin is widely different and which vary in their character.

Ziegler has long ago demonstrated the peculiar renal fibrosis resulting from peripheral arteriosclerosis. In old age, where it is not uncommon to have various arterial tracts severely involved in sclerosis and in which the lumina of the vessels are distinctly impeded, atrophic changes result in the area supplied. It is obvious that the amount of sclerosis varies greatly and is bound to pick out limited areas. The kidney tissues which suffer from the circulatory disturbances undergo atrophy and even complete loss without, however, necessarily showing evidence of intracellular degenera-

tion (fat) as is otherwise so commonly met with. The kidney shows areas of sharp depressions scattered irregularly over its surface so that its structure and shape are distorted. The individual depressions simulate those of infarct, but microscopically may at times be distinguished from these in that the involved areas contain some of the parenchymatous structures not completely destroyed. Furthermore, the kidney capsule is rarely adherent and the cortical surface between the areas of depression is relatively smooth.

Such depressions are the result of the obliteration of a fairly large vessel within the kidney. At times, it may be, smaller vessels involving more restricted portions of the kidney are affected. This then leads to a local fibrosis of the glomeruli supplied by this circulation. Under these conditions, the process, both in the glomeruli and tubules, is one of slow and progressive degeneration with a secondary replacement fibrosis. It is unusual to observe under these conditions any evidence of an inflammatory reaction.

Compared with the granular contracted kidney, these changes in the arteriosclerotic kidney are quite different. It is inconceivable that a process of arteriosclerosis could so uniformly effect so many arterioles of a constant caliber to give the character found in the uniformly granular kidney. A comparable picture is to be observed in no part of the body and we are well aware how uncertain is the distribution of arteriosclerosis. As the fibrosis following upon processes of degeneration in the atrophies of vascular scleroses is without inflammatory response, one misses entirely the presence of a granulation tissue and subsequent adhesions. The absence of these is noted in the freedom of the kidney capsule and in the lack of synechiæ about the glomerulus. Frequently, too, Bowman's capsule shows no thickening. Ziegler truly calls this the senile kidney.

It is, however, not common to meet with a clear-cut and uncomplicated case. The vascular scleroses of the kidney are most commonly the result of the same influence which has produced a primary inflammatory lesion in the kidney stroma. Hence, the development of scar tissue in the renal structures goes hand in hand with renal arteriosclerosis. Here, however, in the early stage, as well as

during the years of progressive involvement, the kidney tissues and arteries show the presence of inflammation. These inflammatory deposits are easily recognized and obviously vary in amount at the different stages. Jores has seen them in his interstitial nephritis but has taken the view that no relation between the arterial disease and the inflammation can be determined. Like the results of the streptococcus viridans infection upon the heart giving rise to inflammatory processes differently disposed, so too, this same infection which is so frequently at the bottom of the fibrosis of the contracted kidney, brings about inflammatory reactions of varying intensity in different portions of its structure. The arteries appear to form the centre of distribution for these reactions and much of the response is spent in the tissue surrounding the small vessels coursing through the cortex. To a certain extent, however, intimal reactions are also found. The latter, however, arise somewhat later in the course of the kidney disease, so that examples are not difficult to demonstrate in which intimal sclerosis is wanting while a non-suppurative inflammation is active about the vessel. Later, however, the picture is reversed and the intimal sclerosis attracts our eye. This is now the stage when appearances suggest that a close relation of cause and effect exists between the intimal arteriosclerosis and the renal fibrosis.

The intimal disease of the arteries most commonly met with in the late stages of chronic interstitial nephritis consists of a chronic endarteritis with deep fatty change. The presence of a true hyperplasia of the musculo-elastic layer with secondary degeneration of the inner muscle bundle has never been met with by us, nor have its advocates ever clearly demonstrated its presence. The finding of splitting of the internal elastic lamina is now found to have no specific bearing on the problem of arteriosclerosis. McMeans, of our laboratory, has shown that such splitting is the common occurrence during inflammatory reactions of the intima.

Granted, therefore, that the early reactions which lead to the granular contracted kidney, simultaneously involve portions of the kidney parenchyma and its arteries, it is often extremely difficult to distinguish in the late stages of the disease exactly how much of the scar tissue has resulted through inflammation or as replace-

ment fibrosis following arteriosclerotic atrophy. We should, however, continue to distinguish clearly the arteriosclerotic kidney of Ziegler from the granular interstitial nephritis, the former giving rise to true atrophic processes in the parenchyma with replacement fibrosis, the latter having an inflammatory basis for the development of connective tissue variously distributed about the important structures of the organ.

GELATINOID CARCINOMA (MORBUS GELATINOSUS) OF THE PERITONEUM

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The special interest in this case is concerned with several points: (1) It is an example of ascites existing over a long period and requiring a large number of tappings. (2) The problem of diagnosis. (3) The character of the peritoneal fluid. (4) The interpretation of the autopsy findings.

The history is as follows: G. B., a colored man, aged thirty-eight years, a butcher by occupation, was admitted to the Jefferson Hospital first on February 21, 1911.

Family History. His father died at fifty-eight years from asthma, his mother at sixty years, the cause not being known; he has six brothers and sisters living and well; one died from an accident and one from typhoid fever. There is no history of tuberculosis.

Personal History. Measles, mumps, and chicken-pox in childhood were the only infectious diseases. There is no history of cough or shortness of breath. The appetite and digestion have been good. There was no history of any illness suggestive of appendicitis. There is no note of any urinary trouble. He had a gonococcus infection at the age of eighteen, but gave no history of a luetic infection. The patient had used only small amounts of alcohol.

Present Illness. In the summer of 1910 the patient noticed there was some enlargement of the abdomen. This occurred without any pain or disturbance of the stomach or bowels. The distention did not last long and the patient states that it disappeared entirely. In January, 1911, the swelling of the abdomen returned and increased gradually until he was admitted to the hospital. There had been no pain, and the patient com-

plained only of discomfort when coughing or stooping over. He had some shortness of breath on severe exertion, but worked until five days before admission. Otherwise he had been in good condition and did not complain of any gastric or intestinal trouble.

Examination. The patient was well nourished. There was no definite jaundice. The lungs showed dullness at both bases and the heart was displaced upward. These were both regarded as being due to the pressure from the abdomen. The abdomen showed very marked enlargement and the usual signs of ascites. The liver and spleen could not be felt. There was no edema of the scrotum and very slight edema of the legs. The blood count showed hemoglobin, 68 per cent.; reds, 4,900,000; leukocytes, 7400. The urine had a specific gravity which varied from 1.015 to 1.030, and generally contained a small amount of albumin, but was otherwise negative. The abdomen was tapped and about nine liters of fluid removed. This presented the usual appearance of ascitic fluid, and was not peculiar in any way. The specific gravity was 1.030, and there was a considerable amount of albumin. The majority of the contained cells were lymphocytes. After the tapping the fluid reaccumulated for a time and then diminished. He was discharged with evidence of some fluid in the abdomen, but in good general condition. The picture at this time was apparently that of cirrhosis of the liver with ascites.

During the following three years the patient was admitted to the hospital seventeen different times. It does not seem necessary to mention these in detail, and only the important points are given, which, for convenience, may be put under separate headings.

General Condition. The patient's general health remained extremely good. The only complaint which he made on each return to the hospital was of the abdominal distention. It was only on his last admission, March 4, 1914, that any change was noted. He had then lost weight and was suffering from frequent vomiting, which apparently prevented his getting sufficient nourishment.

Abdominal Condition. This was much the same on each admission. The degree of distention varied somewhat, but was always quite marked. The usual physical signs of ascites were always present. There were no signs suggesting any disease of the gall-bladder, appendix, or cecum. Examination of the rectum did not show any abnormality.

Abdominal Tapping. Up to the time of his last admission he had been tapped fifty-eight times. On forty-six occasions fluid was obtained, the amount of which varied from 2500 c.c. to 10,560 c.c. During a period of about three years from the onset he was tapped nine times and the fluid had always the same character as noted on the first occasion. On the tenth tapping (May 22, 1913) a different state of affairs was found, which will be referred to later. One curious point was that on several occasions he was

much better after an attempted tapping which was not successful. On two admissions there was no successful tapping, but the patient was discharged very much improved and with the distention lessened.

The patient, naturally, became an authority on the methods of being tapped, and always graded the different house officers, under whose care he came, according to their ability to tap. He emphasized two characteristics which the trocar should have, namely, that it should be sharp and of large size.

On May 22, 1913, there was a distinct change in the material obtained by tapping. On this occasion a number of gelatinous masses escaped with the ascitic fluid. This was about three years after the onset and about one year before death. These gelatinous bodies varied in size from about the size of a grain of wheat to an ordinary pea; occasionally larger masses were obtained. Their appearance was gelatinous and in some ways rather suggested boiled tapioca grains. The larger masses that were obtained had much the same appearance. Occasionally the trocar was completely blocked with these, but, as a rule, they did not interfere materially with the tapping. About a month later, as tapping was again required, it was thought well to do an exploration, and a small incision was made in the abdominal wall. A large quantity of fluid was obtained and the same gelatinous colloid-like material. The opening was not large enough to permit of any extensive investigation of the abdomen, but nothing abnormal in any of this viscera was noted through the small incision. The fluid at this time showed 83 per cent. of small lymphocytes, 11 per cent. cells with large nuclei, and the remainder polynuclear cells and others difficult to classify.

The problem of diagnosis was a most interesting one. The patient had chronic ascites, but his general condition was excellent and there was no jaundice. In August, 1913, the abdomen was markedly distended, with definite evidence of ascites, but this was not extreme. For the first time enlargement of the liver was found and the edge of the left lobe was felt in the midline 3 cm. above the navel. It seemed quite distinctly irregular. It was not possible to feel the edge of the right lobe with certainty. The spleen was considerably enlarged and readily felt below the costal margin. In view of the long duration of the ascites, the fact that it had come and gone, the patient's excellent general condition, and the enlargement of the left lobe of the liver and spleen, the question of syphilis of the liver had to be considered. However, the Wassermann reaction was always negative and no signs of syphilis were to be found unless the abdominal condition was due to it. Still it seemed worth while to let the patient have some potassium iodide, and it was begun at this time. We never felt sure that it made any difference, although the patient claimed that after taking it the fluid accumulated much more slowly. During this admission the

patient was tapped a number of times, the fluid always containing the same gelatinous masses.

Examination of the cells in the ascitic fluid showed considerable variation in the percentage of lymphocytes at various tappings, and also in the occurrence of eosinophiles. At this time (August, 1913) it was not possible to be certain that the right lobe of the liver was enlarged, but a little later this was definitely made out, and in January, 1914, the edge in the right nipple line was felt 10 cm. below the costal margin. The enlargement of the left lobe previously noted was still present. So far as we could determine there had been a definite increase in the size of the right lobe. In view of the fact that he had been taking potassium iodide quite steadily for some months, this was strongly against the possibility of the enlargement of the liver being due to lues. The last admission was on March 4, 1914. By this time his general condition showed marked change, shortness of breath and edema were more marked, and he had been much troubled by vomiting. Examination of the stomach contents did not show anything of special interest except that no free hydrochloric was obtained. The blood showed only a moderate secondary anemia; the differential count was normal. The obstinate constipation which he had on admission was soon replaced by persistent diarrhea. We tested the length of time which it took for material to pass through the bowel and found that this was usually about four or five hours. When the condition of the intestines was seen at autopsy this seemed very remarkable.

The difficulty of tapping increased so that sometimes it was necessary to tap in several places before we could obtain any fluid. There were eleven successful tappings on the last admission. At times he complained of severe abdominal pain, but did not show any marked tenderness. It was not possible to feel either the liver or the spleen at this time. About two weeks before death a number of *nodular masses* were felt in the abdomen. These were evidently in the peritoneal cavity, felt quite superficial, were very hard, and quite freely movable. They varied in size from a diameter of about half an inch to perhaps one and a half inches. They were felt in different places on different days. The vomiting and diarrhea continued until death on May 7, 1914.

The main facts may be summarized as follows: A male, aged forty-one years, with chronic ascites for four years and fifty-seven successful tappings. For three years the fluid showed no peculiar features and then gelatinous colloid-like material appeared and was present for a year until death. During the greater part of this time the patient's general condition was excellent. The liver and spleen showed enlargement at one time and later became reduced

in size. Shortly before death many hard, rounded, movable masses were felt in the abdomen. There was intractable diarrhea for the last few weeks of life.

The gelatinoid material was studied in the laboratory of our colleague, Professor Hawk. It was a mucin-like substance, much like the material known as serosa mucin. It contained 11.5 per cent. of nitrogen and 0.8 per cent. of sulphur.

The question arises as to the course of events, and it must be confessed that the autopsy did not throw much light on this. For three years the patient had ascites regarded as due to cirrhosis of the liver. But cirrhosis of the liver without some other condition does not, as a rule, permit of repeated tappings over such a long period, for ascites is usually a terminal event in pure cirrhosis. With the appearance of the gelatinoid material in the ascitic fluid the question arose whether the process had been of a malignant character from the onset. If so it must have been extremely mild. The presence of ascitic fluid with the characteristics of that found in cirrhosis of the liver has been noted for some time before the appearance of signs suggesting a malignant process. Thus in the case reported by Pye-Smith, during a period of ten months the patient was tapped seven times and the usual fluid of ascites secondary to cirrhosis was found. On the next tapping cells were found which suggested colloid carcinoma. This was the celebrated case in which tapping was done 299 times. Death occurred after a duration of nearly nine years, and at autopsy a papillomatous tumor of each ovary was found. The peritoneum was thickened and covered with secondary papillomata.

Another obscure point was that three months after the first finding of gelatinoid material the liver and spleen were found to be enlarged and six months later the enlargement was still more marked. Subsequently the liver decreased in size, and before death the liver and spleen could not be felt. There does not seem to be any explanation for the increase in the size of the liver and spleen. The enlargement was not secondary to circulatory failure. The size of the liver at autopsy was proof that we had not been mistaken in the belief that the enlargement had disappeared. In the absence of cirrhosis it seems probable that the decrease in size

of the liver was due to the marked increase in the thickness of the capsule. It may be suggested that the enlargement did not actually exist but the liver was very easily felt after tapping and the increase in size occurred under observation. The position of the upper limit of dulness did not change.

Pathological Report. The body is that of a poorly nourished adult colored male. *Rigor mortis* is present but easily broken up. Pupils equal and contracted. Slight edema of both ankles. Abdomen greatly distended and tense. Subcutaneous fat is very scanty. Abdominal and thoracic musculature is pale red and greatly atrophied.

As matters of special interest pertain to the abdomen a brief survey only will be given to the other findings:

Left pleura slightly thickened; cavity contains a few cubic centimeters of slightly turbid yellowish fluid. Between the lobes of the left lung, situated immediately under the pleura, are several elevated grayish areas, 5 to 10 mm. in diameter, which on section show a lobular arrangement, the alveoli containing a grayish transparent gelatinoid substance. Although the lung appears small it crepitates throughout except a narrow stratum at the base; the lower lobe is also somewhat congested.

Right pleura is dry; the serosa slightly thickened, especially over the base. On the pleural surface of the diaphragm are a few grayish gelatinous bosses and granulations; the largest of the former measures a little over 1 cm. in diameter; the fine granulations may be exudative or neoplastic, of which one cannot be sure. The nodules in the muscular portion of the diaphragm have raised the serosa, which is still, apparently, intact. Except for a few areas of partial collapse and considerable congestion, a large part of which is clearly hypostatic and associated with some edema, the lung is not the seat of any noteworthy abnormality. In neither lung was any secondary growth observed. No metastasis in the mediastinal lymph nodes or other tissue except the subpleural growths already mentioned.

Pericardium uninvolved. Heart is displaced upward and slightly to left. No important lesion. There are a few negligible sclerotic areas in aorta and larger branches.

Except for a mild patchy fibrosis the kidneys are normal. No gross change in adrenals. No noteworthy lesion in bladder or genitalia.

Permission to examine the central nervous system was not obtained.

Abdomen and Contents. As the incision approaches the abdominal cavity it is noted that the parietal peritoneum is thickened, at points almost

[1] Section and preliminary examination made by Dr. E. D. Funk, demonstrator of morbid anatomy, upon whose protocol the following is in part based. Much of the general description deemed immaterial to this presentation is omitted.

leathery, and in such areas resists incision. When the abdomen is widely opened the almost universal presence of a gelatinoid material is observed. It has accumulated particularly in the pelvis, lumbar regions, right and left, and between the stomach and liver. About 2500 c.c. were removed; all that would adhere to visceral and parietal peritoneum was left in position; it was thought that formalin fixation would secure it in place, but to a slight degree only was this result attained. The greatly-thickened parietal peritoneum was dissected loose from the muscles on each side and posteriorly, the diaphragm incised along its attachment to the parietes, and the entire mass removed for fixation and further study. The following data were obtained from examination of the fresh specimen, and later, after formalin fixation, by such dissection as was permissible without destroying the specimen (see Fig. 1).

The upper border of the specimen is formed by the diaphragm, which on the inferior surface is intimately attached to every viscus with which it comes in contact. The attachments to the liver and spleen are particularly firm. The intestines, including the colon, and the stomach are closely packed in the median line and matted together by adhesions, many of which are so firm that the enclosed viscus tears before the adhesion yields. Nothing that could be certainly identified as omentum remains distinguishable in the mass. Between the stomach and liver is a cavity holding more than a liter of gelatinoid substance. This has displaced the stomach downward and rather behind the colon, to which it is firmly attached. The transverse colon is greatly dilated, the dilatations being most marked near the hepatic and splenic flexures. To this part of the colon is also attached the small intestine, heaped in an indistinguishable mass. With a long brain knife the anterior portion was cut away, exposing the opened convolutions of the intestines beneath. With difficulty these were separated above, as shown in the illustration, to permit palpation of the pancreas, which does not appear changed. The caput coli is greatly dilated and the wall slightly thickened. The outer aspect of the caput coli and a part of the descending colon and sigmoid are attached to the parietal peritoneum. The ascending colon passes mesially almost to the midline behind the small intestine and ascends tortuously to the hepatic flexure. A similar mesial displacement of the descending colon is also present. Apparently these displacements are due to pressure of gelatinous masses occupying the lateral aspect and lumbar region of the abdomen. The area of the gall-bladder and pylorus is occupied by a dense fibroid mass containing many small cavities filled with gelatinoid material.

Incision through 5 cm. of this mass opens the gall-bladder; the cavity is 9 cm. long and irregularly compressed with a maximum breadth of 3 cm. It is filled with bile-stained gelatinoid material somewhat thinner than much of that in the peritoneum, but may be scooped out as a semisolid

mass, dark greenish-yellow in color. The mucosa is smooth. The bile ducts were not dissected.

FIG. 1.—Contents of abdomen. Anterior aspect. Carcinoma of peritoneum. Upper margin formed by liver and attached diaphragm. Just below liver. between that organ and stomach, cavity containing gelatinoid material; cavities to right and left and also pelvis contained similar material. Every part of serosa in contact with any other surface is adherent. Some of these adhesions have been broken up. Intestines are rigid and stand open on section. Note nodules on abdominal wall, especially to lower right. For further description see text.

The liver is small, capsule greatly thickened; adhesions practically universal to all surfaces. Several incisions disclosed no secondary growth. Microscopically the cells are granular and shrunken, with a slight increase in fibrous tissue, most notable beneath the capsule.

The appendix was found buried in a mass of adhesions, and though not fully dissected is about the thickness of the little finger and admits a probe 8 cm. The connection with the cecum is closed and the base of the appendix bulges into the cecum as an ovoidal boss 2.2 cm. in diameter. On incision it is found to contain the same gelatinoid material as that present in the abdominal cavity and gall-bladder. The obvious thickening is around the appendix rather than of the appendix; the musculature and mucosa are not thicker than normal, if anything, at least in areas, they appear thin. The great and irregular thickening of the parietal peritoneum is well shown in the illustration. Just below the right lobe of the liver the thickening extends through the peritoneum and into the aponeurosis of the muscle. Neither macroscopically nor microscopically is the wasted muscle found involved. The inner surface of the parietal peritoneum is covered with loosely attached gelatinoid or colloid material; relatively little of this substance is shown in the illustration. There are also, at many points, on the parietal peritoneum and on the adhesions binding the viscera, numerous nodules varying in size from 2 or 3 mm. to 4.5 cm. In the illustration two of these are well shown at the lower right on the parietal peritoneum, and on the mass of adherent intestines in the median line near the lower border. Masses of exactly the same type are also free in the peritoneal cavity; several of these were removed, attached on a frame, and photographed (Fig. 2). Incised in the fresh condition they were found to possess outer capsules 1 to 3 mm. in thickness, and to contain soft gelatinoid material which flowed from the cut sufraces with about the same consistency as thick egg albumen. Fixed in formalin they retained their contour and bore incision without loss of contents. Several of those shown in Fig. 2 exhibit the essential morphology. Running in from the capsule are numerous fine delicate trabeculæ without regularity of arrangement, forming a sort of a reticulum, in the meshes of which is contained the gelatinoid substance. Numerous histological sections show these to be composed of imperfectly-developed fibrous tissue containing a few round cells, an occasional leukocyte, and homogeneous staining gelatinoid material. In none of the sections was any epithelium encountered. It was evidently these structures that could be palpated through the abdominal wall during life. Several were still loosely attached and apparently about to separate from the wall or the visceral mass. Examination of one of the attached masses seemed to indicate that they arise from condensation of the gelatinoid material which later becomes edematous, the characteristic cellular elements disappearing.

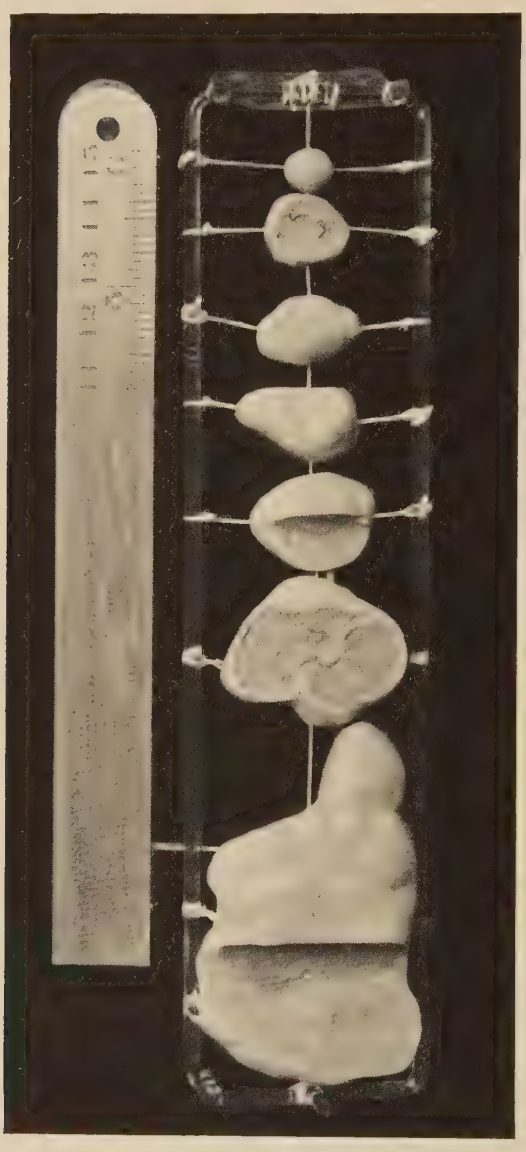

FIG. 2.—Nodules from peritoneum. Many of these, of practically every size, the largest 5 cm. in diameter, were free in the belly cavity or loosely attached, often by a thin filament only, to the abdominal wall. Those shown were all free. For further description see text.

Their development is entirely internal to the structure that was thought to occupy the position of the normal peritoneum. Ssobolew observed similar bodies.

FIG. 3.—Section of parietes. Abdominal wall immediately below liver mass. Photomicrograph. *A*, muscle of abdominal wall; *B* to *C*, muscle fascia, extra-peritoneal tissue, and peritoneum in single thick layer of dense fibrous tissue, at points separated by interstitial edema; *C* to *D*, stratum in which neoplastic growth is at points demonstrable. Just above leader from *C*, stratum of columnar epithelial cells, most of which are of the tall pallisade type. Note that just beneath epithelium edema is marked; *D*, and above, reticulum partly enclosing spaces containing homogeneous gelatinoid material; *E*, space clearly outside peritoneum; a few disappearing epithelial cells along upper margin, others below; space filled with gelatinoid substance; square outlined in centre is shown under higher magnification in Fig. 4.

Morbid Histology. Sections of the organs are for the most part without interest. Several of the gelatinoid masses removed at operations and others obtained postmortem, were fixed and stained by appropriate methods without disclosing any cellular element upon which a histological diagnosis could be based. Similar disappointing results were obtained from numerous examinations made of parts removed from several areas in the parietal

FIG. 4.—Small central area from Fig. 3 more highly magnified. Photomicrograph. In centre papillary growth covered with tall columnar epithelium; many cells are of the chalice type. Part of another papillary growth is shown at left. To right note regressing epithelium; edema at base of papillary mass and beneath palisade epithelium.

peritoneum and from the thickened masses of adhesions. Most of these showed an exceedingly edematous fibrous reticulum obviously in various stages of formation. The general character of the histological appearance may be gathered from a close study of the photomicrograph shown in Fig. 3, which includes the edge of the abdominal muscle below; above is the denser fascia, the peritoneum showing the neoplastic involvement, and at

the top the reticulum surrounding irregular communicating spaces containing the homogeneous, almost cell-free, gelatinoid substance. It will be observed that the latter contains a scanty cellular detritus and nothing upon which a histological diagnosis as to the character of the process could

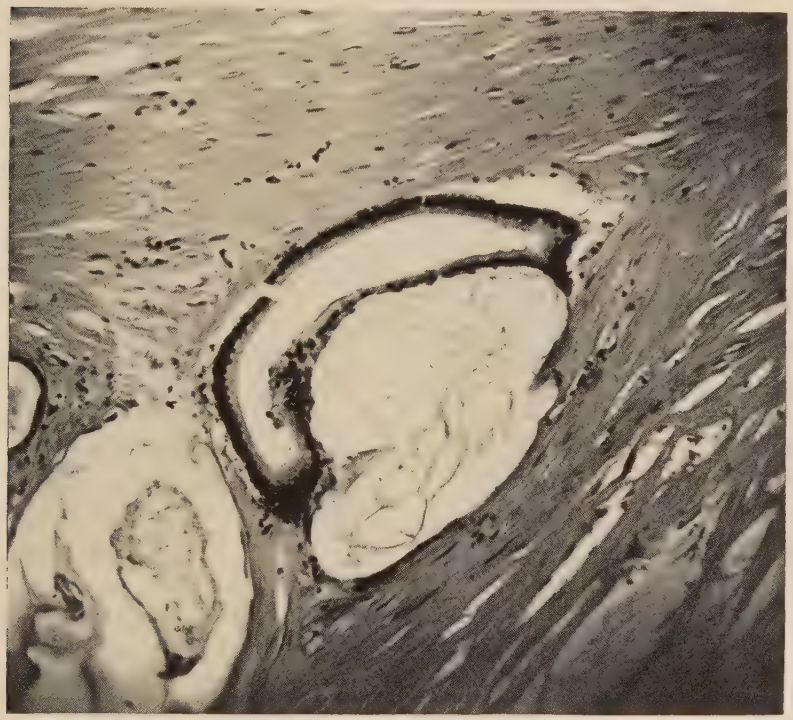

FIG. 5.—Section from fibrogelatinoid area in gall-bladder region. Photomicrograph. Typical epithelial lined space showing regression of epithelium and edematous gelatinoid substance arising beneath the epithelial cells; over this substance the epithelium is disappearing. Below and to left (left lower corner) is a mass of gelatinoid substance containing two regressing epithelial cells. It has not been possible with certainty to determine the origin of this gelatinoid substance. Just below centre of left margin part of vessel in stratum of fibrous tissue. A few fibroblasts and an occasional leukocyte may be recognized.

be based. However, in the examination of a large number of sections numerous pictures similar to that shown in the centre of the field were encountered. Note the papillary growth projecting upward surmounted by tall columnar epithelium the cell nuclei of which are marginated immediately at the bases of the cells. The higher magnification of this same

area is shown in Fig. 4. Many of the epithelial cells are of the chalice type. The connective tissue immediately underlying the cells is, in practically every instance, obviously edematous, and apparently when the edema reaches a certain stage the cell disintegration begins and continues until the epithelium entirely disappears.

The morphology and chemical reactions of these cells are identical with those observed in the palisade epithelium commonly found lining the varieties of ovarian cysts with which this disease is so frequently associated; no one who has examined the structure has any doubt as to the epithelial origin. Identical appearances in growths obviously connected with the appendix have been reported.

In the many sections examined structures possessing the same general characters as those described have been found only occasionally. Such growths, however, have been observed in the extraperitoneal fascia and in the diaphragm immediately beneath both peritoneum and pleura.

The almost universal involvement of every structure in the abdominal cavity in this case, and the absence of any conclusive dominance in one particular area renders impossible an unassailable statement as to the origin of the process. Those who believe strongly in its appendicular relation will lay stress on the fact that the appendix is involved. An examination of Fig. 1 must impress the observer with the fact that the gall-bladder area is conspicuously affected. At this point the colon, gall-bladder, intestine, pyloric complement of stomach, diaphragm, and abdominal parietes are implicated. If finding gelatinoid material in the cavity of a viscus could be taken as proof of origin in that organ, there would be some ground for the statement that in our patient the process might here have arisen in the gall-bladder. Had the primary lesion been in the appendix one would not have expected so extensive an involvement of the upper abdomen. Of course, without more detailed section than has been made it has been impossible to exclude the stomach, duodenum or pancreas, or indeed for that matter almost any part of the intra-abdominal alimentary canal. It is quite certain that such a tumor might have originated in a diverticulum. In the absence of later and more exact infor-

mation concerning the nature of these growths the condition would probably have been regarded as a primary neoplasm of the peritoneum; this possibility, we think, may be excluded.

Of special interest is a consideration of the nature of the process concerning which many views have been held. Pean, forty-five years ago, applied the term gelatinous disease of the peritoneum, fully recognizing and admitting the vagueness of the term. In some form no doubt this was what Virchow called colloid cancer, and to which has also been applied the terms mucoid cancer, gelatinous ascites, and carcinomatous ascites. Werth, in 1884, introduced the name pseudomyxoma, to which there are many objections, but which unfortunately has been widely adopted, and under which name most of the cases are recorded. We believe the process is neoplastic and essentially cancerous, but would manifest no particular preference between the terms colloid, mucoid, muciparous, or gelatinoid carcinoma, if anything, inclining toward the last. The designation "maladie gelatineuse" is not inappropriate. Failure to recognize the carcinomatous nature of the process rests upon the fact that endless search or exceptional good fortune in any particular case may be necessary to locate the areas of definitely cancerous morphology. The fact that invasion extends through the peritoneum into the muscle fascia, through the diaphragm from serosa to serosa, with the formation of subpleural nodules, the nodules between the lobes of the lung, and other evidences seem to us difficult of explanation except on the assumption that the process is potentially malignant.

The universality of the retrograde changes in the epithelium, not commonly encountered in cancer, is due to some influence which our study has failed fully to disclose. Apparently the proliferating epithelium is encountering some antagonistic influence that is constantly breaking it down. The epitheliolytic agent seems to be of humoral origin. No evidence of phagocytosis, no noteworthy leukocytic infiltration, no giant cells, are present, but an edema, in which the epithelium seems to undergo disintegration and solution without leaving behind the usual detritus incident to chromatin fragmentation commonly observed in the presence of a necrosis and cell disintegration. In Fig. 5 it can be noted that beneath the

epithelium on the under side of the space lined by cylindric cells there is a collection of edematous gelatinoid material over which the epithelial cells are manifesting retrograde changes. In a space below and to the left the epithelium has almost completely disappeared, and this retrogressive change on the part of the epithelial cells is manifest in almost every location where they are found. The influence that brings it about seems to come after the cell is growing or in some instances after the cell is fully grown, suggesting that the growth of the cell is necessary for its appearance. Following conventional usage it would be easy to suggest a name for such a hypothetical body; at the risk of being prosaic we forego this.

It is well established in this class of cases that complete removal of early manifestations may be curative, and that admittedly incomplete excision of advanced lesions may be followed by long intervals before recurrence takes place and in some instances apparent recovery. Such cases have been recorded by Lejars, Trotter, Neumann, Eden and others. In one of Lejars's cases the tumor disappeared. In Eden's patient gelatinous disease due to an ovarian tumor was present at operation done "several months" after appearance of symptoms; the ovary and a large part but not all of the jelly were removed; three months later the patient was well. Two years and four months after the first operation the other ovary and appendix were found involved and removed. Nearly two years later the patient was reported well. According to Lejars, lesions of ovarian origin are more malignant than those arising in the appendix.

Destructibility of cells composing or derived from malignant tumors has been established by numerous observers, and more recently has been especially investigated by Iwasaki. Twenty years ago Goldmann suspected the presence of some protecting body. Hodenpyl's results obtained by injecting ascitic fluid derived from a patient with cancer aroused hopes that have not materialized. Our case and many in the literature more than suggest the existence of some such body and of tissue and humoral potentialities that we may in the future find some way to mobilize. The peritoneum may be able to produce such an agent. Bland-Sutton says

"large numbers of cancer cells which are shed into the abdominal cavity perish, for the peritoneum exercises defending or prophylactic power against such marauders." We know that tissues engaged in processes essentially protective in nature suffer, often are almost destroyed when the fight is lost; note the lymph-nodal changes in many infections, such as plague and tuberculosis, the liver necroses in infections and intoxications and consider the destroyed omentum in some of these peritoneal neoplasms. Possibly that organ of inconclusively-established function may be playing a part of which we know nothing. According to Theilhaber there are on record 200 cases of cancer spontaneously cured. Coley's results in sarcoma cannot be ignored. The problem is to determine by what mechanism the result is attaihed.

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DISCUSSION

Dr. Louis B. Wilson: I would like to suggest that, for the sake of accuracy, it might be well to abandon the word colloid and adopt mucoid for the designation of this form of cancer.

Dr. David Riesman: There was recently in my wards at the Philadelphia General Hospital a woman with gelatinous carcinoma of the peritoneum, which had its origin in a fungoid tumor of the rectum. Although the history indicated a rather acute condition in the abdomen, the mesentery and omentum were enormously thickened by an infiltrating, gelatinous growth. The peritoneum pretty generally throughout the abdomen was covered with succulent nodules. The solid viscera, however, seemed practically uninvolved; there was but a single growth in the liver. The whole appearance was that of a surface implantation.

Dr. W. M. L. Coplin: With regard to the proper designation of the neoplasm, collogen and precollogen were just as abundant as mucoid. It is doubtful whether either term is properly designative.

OCCUPATIONAL INJURIES DUE TO RADIUM: PERSONAL EXPERIENCE, WITH REPORT OF CASES

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Introduction. During the past two years the Cancer Commission of Harvard University has been engaged in obtaining data concerning the therapeutic value of radium. Owing to the great variety in the type of lesions to be treated and in their distribution the methods of application have been varied, chiefly as to difference in filtration and protection. This has necessitated in the application the frequent manipulatuon of highly radio-active tubes and applicators.[1]

Rutherford[2] states that "Walkhoff first observed that radium rays produce burns of much the same character as those caused by Röntgen rays. Experiments in this direction have been made by Giesel, Curie and Becquerel and others with very similar results. There is at first a painful irritation, then inflammation sets in, which lasts from ten to twenty days. This effect is produced by all preparations of radium, and appears to be due mainly to the α and β rays. Care has to be taken in handling radium on account of the painful inflammation set up by the rays. If a finger is held for some minutes at the base of a capsule containing a radium preparation, the skin becomes inflamed for about fifteen days and then peels off. The painful feeling does not disappear for two months."

[1] Ordway, Thomas. The Use of Radium in Cancer and Allied Conditions at the Huntington Hospital—Illustrative Cases. Boston Med. and Surg. Jour., 1914, clxxi, pp. 771–783.

[2] Radio-active Substances and Their Radiations, Cambridge University Press, 1913, p. 327.

Although these rather *acute* reactions due to radium are apparently well known to *physicists* working with radio-active substances and considerable experimental work has been done on animals by biologists very little attention has been paid to the more chronic changes. The purpose of this paper is to record a detailed description of symptoms and signs from the clinical point of view and to emphasize the importance of these as occupational injuries so that more serious effects may not result in those engaged in the application of radium as a therapeutic procedure.

Personal observation in London and Vienna and in Germany while investigating the status of clinical work with radium had called attention to the possibilities of discomfort and injury from contact with radio-active substances.

In London at the Radium Institute the plan was adopted of rotation in service each month for the nurses handling the applicators. Attention had been called to the effects on the fingers of those handling the radium by sensory disturbance in the form of pain and anesthesia first noticed by the difficulty experienced in preparing eggs at the table according to the English custom. This may seem a trivial instance but it well illustrates a peculiar sensitiveness to heat and the difficulty of delicate manipulation with the affected fingers.

On the other hand severe injury was observed in Vienna in the case of one who has handled large quantities of radium. The thumb, fore- and middle fingers of the left hand showed severe lesions, particularly in the form of atrophy and intractable ulceration.

In Paris at the Laboratoire Biologique du Radium particular inquiry was made as to the effect of radium on the hands and it is interesting to note that one of the attendants who had been making almost daily surface applications for over two years had up to that time experienced no injurious effects whatever. This is probably due in part to the type of applicators used in this clinic.

From this it will be seen that injurious local effects were anticipated so that the changes to be described were not acquired unwittingly but in spite of caution. The increasing use of large quantities of radium warrants a detailed description and record of

these changes, not only because of the annoyance and discomfort caused, but as a warning from analogy to the *x*-rays of more serious late effects, such as atrophy, intractable ulceration and even cancer. Already in certain instances there has been caused not only great annoyance from discomfort but actual impairment in manual dexterity in performing delicate manipulations because of persistent local anesthetic effects.

Throughout the first year of the radium work at the Huntington Hospital a considerable proportion of the applications were made by the physician in charge. As a result of manipulation due to the clinical applications of radium in the variety of cases above referred to a few weeks after beginning there was noticed slight though gradually increasing sensory disturbance in the finger tips, particularly on the ulnar side of the first phalanx of the thumb and the radial side of the terminal phalanges of the index and middle fingers of each hand.

These symptoms occurred very insidiously and consisted of blunting of sensibility of the finger tips, paresthesia such as increased sensitiveness to heat and pressure, amounting at times to actual pain, and anesthesia of varying degree.

The subjective disturbances were out of all proportion to the objective findings which included flattening of the natural ridges on the affected fingers with consequent changes in the characteristic markings of the finger prints, thickening of the horny layer of the epidermis with scaling in varying degree, failure of the tips of the fingers to resume their normal shape after pressure, a sort of pitting, upgrowth of the cuticle at the base of and underneath the nails which were easily cracked, extremely brittle and tend to stand off from the fleshy part of the fingers.

Each assistant and nurse before engaging in the clinical application of radium was warned of the annoying and possibly dangerous effects and told not to handle the active tubes of emanation with the fingers but to make use of forceps. In spite of this a certain amount of handling was unavoidable in changing the radium tubes for suitable filtration and protection in the different cases.

Nurses and assistants, also members of the Commission, have been asked to describe carefully and independently the subjective

and objective changes produced. The onset, variety, and annoyance of the effects may be best understood and appreciated by the individual descriptions to be cited, for the most part in the sequence of their occurrence.

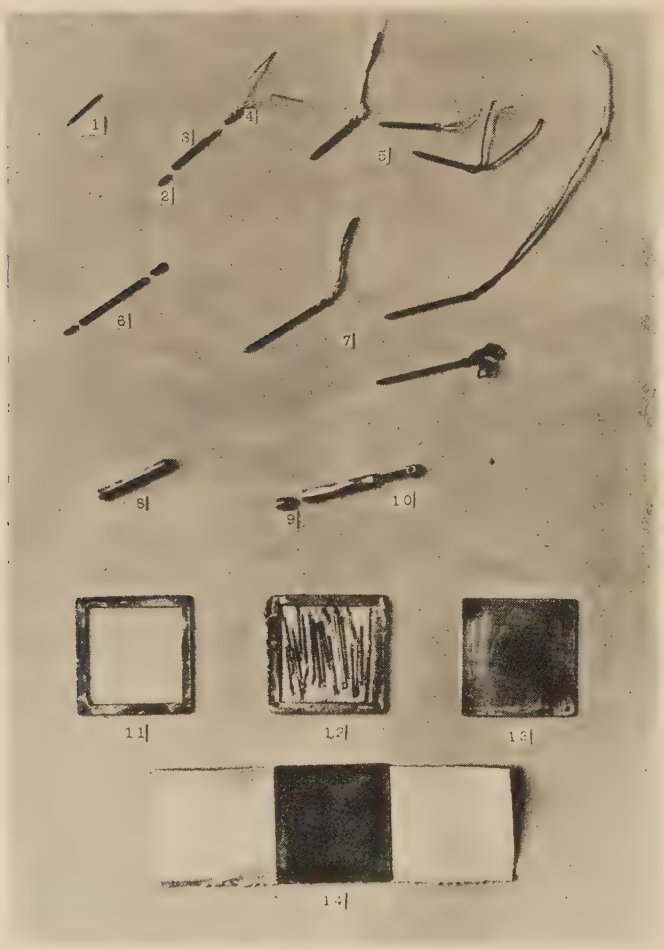


FIG. 1.—Applicators utilized in routine radium treatment. (Two-thirds natural size.)

CASE I.—Physician, C. O., 15, 20, began making routine applications of radium during the early part of November, 1913. These continued

in increasing numbers until the latter part of January, 1914. Since that time applications in special cases only have been made.

After a few weeks the tips of the thumbs, particularly toward the ulnar side, and the fore, and middle fingers, especially toward the radial side,

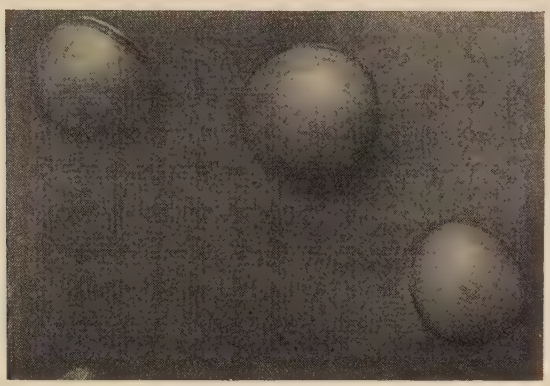


FIG. 2.—Case I. Photograph showing the free edge of the nails standing away from the fleshy part of the finger tips and also indicating the up growth of horny skin beneath the nails. Compare index and middle with ring finger.

gradually became numb and felt unnatural from the blunting of sensibility. They were very tender on pressure so that buttoning small buttons was not only difficult because of the anesthesia but it was painful. Hyperesthesia

FIG. 3.—Case I. Photograph showing the tip of the thumb remaining indented after pressure—indicating the hardening and "empty" feeling of this finger—a late effect—moderately anesthetic.

was also noted in a markedly increased sensitiveness to heat. There was paresthesia in the form of a peculiar unnatural feeling of the finger tips and awkwardness in using the fingers for delicate manipulation. Because of the anesthesia small objects were frequently dropped and

difficulty was noted in taking pulses with the affected finger tips which are those commonly used. These subjective symptoms have been very pronounced, persistent and out of all proportion to the objective findings.

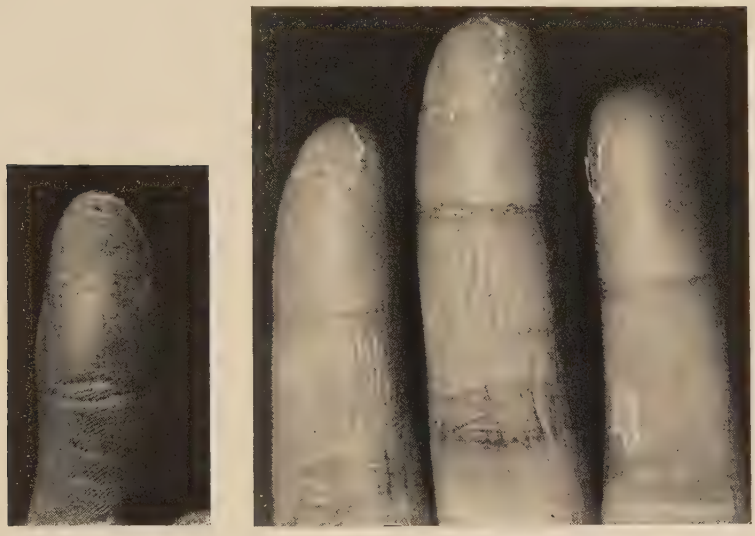
The affected portions of the fingers above described became smooth and shiny, the ridges giving the characteristic finger prints became less marked and almost obliterated (Figs. 6 and 8). Later the epidermis was thickened, dry and parchment-like and on pressure the pad of the finger tip remained indented for some seconds instead of immediately resuming its rounded form (Fig. 3).

The thickened horny layer became wrinkled and cracked and scales of varying size repeatedly desquamated. The nails stood off from the fleshy part of the affected fingers, and there was a marked tendency for the upgrowth of the tissue beneath the nail (Figs. 2 and 5).

At the present time, although actually handling the radium for clinical application but occasionally for almost a year, the pain tenderness and sensitiveness to heat and the objective signs have largely disappeared, notwithstanding this interval the dryness, parchment-like feeling, partial anesthesia and slight tenderness of the affected finger tips persist.

Case II.—Nurse, C. O., 15, 21, began making routine applications of radium in December, 1913, continued this until the last of February, 1914. After that time occasional applications were made with an interval of three months on vacation. "Two weeks after first handling the radium tubes dryness of the skin was noted. A little later the flesh on the finger tips of both hands, especially the thumbs and forefingers, looked yellow and was easily indented on pressure. In about a month the skin over the finger tips began to crack and peel and the dryness of the skin extended down the fingers to the palms of the hands. The flesh grew more rapidly than normally at the base of and below the free edge of the nails which became very brittle. Numbness developed in the finger tips of both hands, awkwardness in picking up articles, pain on buttoning clothing, sensitiveness to heat, later hot throbbing sensations extending the entire length of the fingers on handling radium. At present there is no tenderness but marked paresthesia and slight anesthesia, slight peeling, dryness and marked numbness of the tip of the thumb, index and middle finger of each hand. Great annoyance is caused and difficulty in delicate manipulations."

Case III.—Nurse, C. O., 15, 22, began making routine clinical applications of radium in February, 1914, and continued until June, 1914. "After a few weeks the tips of the fingers became yellowish-white, gradually growing whiter until the fingers looked as if they had been burnt. The skin about and under the nails hardened and grew thicker. The fine lines on the finger tips began slowly to disappear leaving the tips tight, white and swollen. The finger tips remained white and minute cracks appeared. Then from the whole tip of the fingers the skin peeled off leaving the ends smooth, pink and shiny (Figs. 4 and 4*a*).



FIGS. 4 and 4A.—Case III. Photograph of thumb, index, middle and ring fingers of left hand, showing the scaling of the thickened superficial layer of the skin on the radial side of the terminal phalanges and also a similar small area on the second phalanx of the ring finger.

FIG. 5.—Case III. Photograph showing the flattening of the ridges of the tips of the index and middle fingers of the left hand and particularly note how the free ends of the nails stand away from the fleshy part of the finger tip, also note on the forefinger the upgrowth of the skin beneath the nail.

"The tips of the middle finger and thumb of the left hand again became swollen and hard; the thumb appeared yellow as if calloused; the skin is dry and cracked and there is a spot on the thumb 1 x 2 cm. that is red and smooth where the upper layer of skin is cracked and peeled off.

"The left forefinger is swollen, hard and yellowish brown with minute cracks as if the skin were too tight, the fingers are not wholly straight but curved a bit toward the palm. The nails seem to stand out from the fingers (Fig. 5). The cuticle is dry and white, cracked in some places and inclined to grow down around the nail. The finger tips dent on pressure.

"Subjectively it is noted that the fingers were sensitive to pressure especially on the nail. They gradually became stiff and were tender on bending. Definite pulsation was felt about a month after first using the radium. The fingers were very hot and felt much as a mildly septic finger feels; they gradually became oversensitive to heat and the sense of touch was not so sure. Articles would drop from the fingers.

"This has been persistent up to the present time and it is hard to pick up pins or button anything. Pressure on the nail and on the very tip of the finger is painful. The fingers feel very hard, stiff and awkward. It is difficult to tie and loosen hard knots. The hand is dry, rough and feels big."

Case IV.—Assistant, medical student, C. O., 15, 23, began making routine clinical applications of radium, June 3, 1914. "The work consisted in transferring glass capillaries of emanation from one steel jacket to another, or to flat applicators,[1] in fixing silver sheaths over the steel, in arranging a number of steel tubes between pieces of lead, paper and gauze and then wrapping all together in rubber sheeting and adhesive. Tubes of emanation were also placed in various special applicators. In unscrewing the tubes they were held in dressing forceps by the left hand and the points and eyes were held by the right hand occasionally between the thumb, and forefinger, but almost always straight half-length hemostats. The applicators were held in the left hand and fastened with adhesive by the right hand. Glass capillaries have never been picked up or held by the fingers and only rarely in the early part of the work were the steel tubes so held and then for not more than a few seconds. The number of applications per day has varied from five to sixteen, average ten. This indicates approximately the number of times a day that the tubes were handled or changed.

During the first three weeks there was no noticeable effect. Then gradually the tips of the thumbs and index fingers assumed a smooth, shiny appearance with flattening of the ridges (Figs. 6 and 8). This became noticeable at the end of the fourth week. Up to this time there was no unusual sensation. During the fifth week a very thin layer of epidermis loosened and peeled off the tips of the thumb and index fingers from the nail to halfway to the second phalanyx; this scaling took a week during which the

[1] For illustration of these applicators see Fig. 1.

finger tips affected became somewhat swollen and there was a sense of fulness in them. They were warmer to touch than the other fingers of either hand. There was slight sensitiveness to pressure and a tendency to drop small objects such as pins if picked up in the usual manner. During the sixth and seventh week the fulness and discomfort disappeared. In the eighth week the swelling increased and the skin became tense; the sense of fulness returned and pain was experienced on touching a small object such as the head of a pin. There was also some difficulty in picking up small articles and holding them, especially if not directly thinking of them. After the eighth week of making radium applications a vacation of two weeks was taken. During this time no radium was handled, the outer layer of skin on the affected finger tips again became white, hard

FIG. 6.—Case IV. Finger prints of fingers of the left hand. Note that the characteristic ridges are less marked and show more breaks on the thumb, index and middle fingers, particularly on the extreme tips. Left hand. 1, little; 2, ring; 3, middle; 4, index finger; 5, thumb.

and peeled off, leaving the fingers much more sensitive to pressure, either gradual or sudden, and to heat. Indeed severe pain was felt when taking up a cup of hot coffee, a heated test-tube or on washing the hands in water of such a temperature as was not at all painful to the unaffected parts of the skin.

A similar process of swelling of the finger tips, hardening of the superficial layers, cracking and peeling was repeated in the thirteenth, fifteenth and seventeenth week. Each time during and immediately following the peeling there was marked tenderness and acute pain on striking or pinching any object; occasionally a throbbing sensation, more marked if the arms were hanging down, was felt in the affected fingers. The tenderness was so severe that it was difficult to button small buttons, to tie or untie knots, such as shoe strings and necktie; in one instance a room-mate's assistance was required in undoing a tightly drawn necktie.

At the present time the skin of the tips of both thumbs and index fingers and small areas of the left middle and ring fingers is smooth and shiny, the ridges are flattened or absent and the surface is cracked in appearance. When pressed upon the flesh of these finger tips remains indented for an appreciable length of time. There is no apparent difference in vascularity as judged by their color.

The index finger and thumb of the left hand, which is most affected, are distinctly tapering in contrast to the flat, blunt tips of the other fingers and to their own condition before June 1. On fully extending these two fingers and to a less extent the index finger of the right hand there is a marked pulling sensation at the junction of the flesh and the nail. The finger tips are at the present time only moderately tender.

Case V.—Assistant, medical student, C. O., 15, 24, began making clinical applications of radium July 4, 1914. First noticed slight tenderness in the tips of left thumb and index finger, this gradually increased to pain on touching objects, otherwise there was no abnormal sensation. About August 8, 1914, felt in the finger tips a very distinct pulsation which made it impossible to take the pulse for blood-pressure estimation in the usual way. About this time a slight darkening of the color and numbness was noticed. This involved also the tip of the middle finger of the left hand. The tenderness disappeared but the numbness increased until there was such marked anesthesia that it was impossible to button the shirt without looking because the buttonhole could not be felt with the forefinger or the button with the thumb. The finger tips when pressed upon would retain the impression much longer than usual. About a week later a small white spot appeared on the tips and became almost 1 cm. in diameter, this was picked off out of curiosity, it resembled a callus of the palms. The skin beneath was smooth, bright red to pinkish in color, dry and extremely tender. Three areas similar to this appeared. One cracked open but there was no tendency to bleed. The tenderness was so great that it was necessary to bandage the fingers for a week when the cracked area healed. On the three fingers of the right hand the superficial layer of skin peeled from the tip to the middle phalanx. At present date the fingers appear normal except for smooth, glossy appearance and a tingling sensation which seems to spread over the whole finger tip when a small object such as the head of pin is touched.

Case VI.—Assistant, medical student, C. O., 15, 25. He made no routine clinical applications of radium but on one occasion brought the day's supply of radium emanation from the physical laboratory to the Hospital and thoughtlessly put the active tube in his pocket. "On July 28, 1914, I carried a tube containing 32 millicuries of radium emanation in the left pocket of my trousers for about one hour. On August 4, 1914 I noticed an irregularly oval red spot on the anterolateral aspect of my left thigh. It was about 2 cm. long and 1 cm. wide. At this time there was no tender-

ness. The red spot gradually became tender, at first only to marked pressure and later to a slight touch. The skin in the centre of this spot became yellowish, and by August 12, 1914, there was a yellowish spot surrounded by a red border which faded into the surrounding normal skin.

"At this time the spot was very tender and felt warm. About August 15 the yellowish skin had scaled off, leaving a bright, glistening, yellowish-

FIG. 7.—Case VI.—Showing superficial ulceration on thigh. A reaction from accidental application of radium; due to keeping radium tube (32 millicuries) in trousers' pocket for an hour.

red area (Fig. 7) which soon became covered with a crust. This was frequently rubbed off and reformed, each time being smaller until September 5, when the crust disappeared, leaving a smooth, somewhat glistening area a little more red than the adjacent skin and surrounded by a margin of slight pigmentation. September 28 the redness is gradually fading. December 16 the area is now smooth, white and there has been no tendency for the hair to grow out again."

Case VII.—Physicist, C. O., 15, 26. "My first finger burns from the radio-active substances occurred six or seven years ago, and I do not remember their symptoms in detail. They came from handling large quantities of emanation, 200 to 250 millicuries.

"Since then six of my fingers have been burned six or seven times, severely enough for the skin to peel off. I have noticed the following symptoms in varying degrees of intensity; sensitiveness to pressure and heat lasting several days, sometimes so much that it becomes impossible to button clothes and hold warm eggs. Occasionally there had been continuous dull pain without pressure or heat. Each finger has been slightly red with a small yellowish spot at the point of the most severe burn. After four or five days the pain and sensitiveness passed away, and the fingers gradually become calloused. After several weeks the skin peeled from a considerable area, leaving fresh skin that was quite sensitive for a few days.

Fig. 8.—Case VII. Photograph showing the flattening of the ridges on the tips of the index and middle fingers compared with the ring and little fingers. Left hand.

The lines that previously disappeared returned, and the finger tips were smaller than normal for a time, but gradually filled out. In no case has a finger ulcerated.

There is sometimes a desire to hold the hands closed tighter than they usually rest. On the whole my fingers appear to be less sensitive to touch, etc., than they used to be."

Case VIII.—Physicist, C. O., 15, 27, devotes a part of his time in the laboratory daily to pumping the radium emanation into capillary glass tubes, sealing these into lengths suitable for applicators. During this time the activity is comparatively slight and they are retained in the laboratory three hours until the maximum intensity develops when the measurement of the activity is made. "I so frequently burn the tips of my fingers while blowing glass that I was never quite certain, during the early stages of a radium burn, whether the pain was caused by a heat burn or a radium burn. The two sensations are, however, dissimilar. The pain of a radium burn is not at the surface; it is probably better described as soreness. The nearest approach to it in heat burns are the burns caused by holding a glass tube which is just hot enough to cause a burn after

four or five minutes. Radium burns, like heat burns, are sensitive to heat. I find it difficult to hold glass in the flame for glass blowing. Radium burns are more painful in the morning. I first notice them while dressing. The explanation of this seems to be that they are relieved by massage, manipulation of the flesh removing the soreness. As the burn progresses the skin becomes hard and horny. The surface layers later peel off. It has seemed to me that as the burns are getting well, the burned tissue is not as firm as normal tissue; it feels as if there was a hollow space in the end of the finger. Up to March 26, 1914, I have had seven burns."

Case IX.—Assistant, medical student, C. O., 15, 28. "On September 1, 1914, I first began to use radium, but it was not until October 1 that I began to apply it daily in the routine work of the hospital. From then on to the present time I have done part of the out-patient work and some of the work on the house cases. The applicators used were of all sorts, steel tubes, silver tubes and flat applicators. Knowing the effects on others employed in radium application I have been extremely careful throughout not to unduly expose my fingers, using forceps whenever possible. About December 1 I first began to notice some tenderness in the tips of the index and middle fingers and thumb of the left hand but the index finger was more tender than the others (I am left-handed). A short while afterward the affected finger tips began to feel numb and sensation was deadened as if a finger cot were drawn over each. The finger tips appeared red and when pressed they felt pulpy and when the pressure was removed the skin remained depressed like parchment.

"During the last week of December I accidentally seared the tip of my left index finger with a match. The burn was slight and under ordinary circumstances would have healed in a few days. Contrariwise, in two or three days it began to peel, and by January 1 the whole palmar surface of the terminal digit and on the sides toward the nail had peeled leaving a smooth, reddened surface which was exquisitely tender. It was especially sensitive to heat, warm water almost causing me to cry out in pain.

"Three days ago the left thumb showed a tiny break in the skin on the palmar surface toward the tip of the index finger. Within two days it had peeled off entirely as did the index finger and the symptoms were the same.

"I have had some relief by applications of "white wash" left on over night.

"The fingers of the right hand show slight smoothing out of the papillæ especially on the thumb and index finger but no redness or marked tenderness. The sensation of touch is numbed but not to such a marked degree as in the left fingers.

"It is difficult to state just where to look for the errors in technique to bring about the above burns. At first I thought it might be caused by brief exposures when screwing the eyes into small unscreened steel tubes. The

more likely cause it seems is in putting up special applicators or flat applicators where it is almost necessary under our present technique, to run one's fingers over the tubes or to hold them while a piece of adhesive is being put in place."

Discussion. In these individual descriptions of the symptoms and signs the similarity is striking. In certain instances, however, cases V, VI, VII, VIII the injurious effects were due for the most part to acute reactions, in cases III and IV the changes were chronic with superadded acute, while in Cases I and II there were no acute burns but the changes were the slow and insidious effect of repeated exposures. Indeed in Case I there seems at the present time to be a peculiar susceptibility to slight exposure even after a long interval in which radium has been but rarely handled.

Various general symptoms such as headache, malaise, weakness, undue fatigue, unusual need of sleep, increased excitability, fretfulness, irritability, disorders of menstruation, attacks of dizziness, etc., have been said by Gudzent and Halberstaedter[1] to be caused by repeated and long-continued exposure to radio-active substances. Such symptoms are, however, common in many people at times and as they cannot be accurately and objectively recorded there is doubt if they can be definitely proved to be due to exposure to radium. They may be due to close confinement, tiring routine and lack of outdoor exercise and other causes. The exposures of some of the cases reported were doubtless large; some were assistants in "fabriks" for manufacture of radium apparatus and some had been engaged for years during the entire day in work with radio-active substances. It is therefore probable that certain general symptoms did occur as a result of this exposure. These symptoms, however, will not be considered in this paper.

Changes in the blood of radium workers were observed by Gudzent and Halberstaedter.[2] Most striking was the relative and absolute increase in lymphocytes, 36 per cent. to 63 per cent., average of 10 cases 46.4 per cent.; a relative and absolute decrease in neutrophiles, average 50.3 per cent. There was little change in red

[1] Deutsche med. Wchnschr., March 26, 1914, No. 13, p. 633.
[2] Loc. cit.

blood corpuscles, slight diminution in white cells and the hemoglobin was only lowered in two cases, 70 per cent. and 71 per cent. respectively.

The blood examination in the cases above detailed are recorded in the following table:

BLOOD EXAMINATIONS

Case.	Date.	Hgb.	R. B. C.	W.B.C.	Poly.	Lymph.	Large mono.	Eosin.	Mast cells.
I	Aug. 25, 1914	100	5,300,000	6800	46.3	50.7	2.0	0.8	0.2
	Sept. 3, 1914	94	4,708,000	6900	49.5	47.2	1.0	2.0	0.2
II	Jan. 4, 1915	99	4,464,000	7400	55.5	34.5	7.0	2.5	0.5
III	Aug. 21, 1914	99	4,480,000	7200	60.2	35.7	2.8	0.5	0.8
IV	Aug. 18, 1914	100	5,400,000	9000	73.6	23.6	2.2	0.2	0.4
	Jan. 6, 1915	100	5,108,000	7000	61.0	30.5	7.75	0.25	0.5
V	Jan. 15, 1915	...	5,792,000	8000	64.5	26.0	6.0	1.0	2.5
VI	Sept. 2, 1914	100	4,900,000	5500	53.3	43.8	1.4	0.7	0.8
VII	Aug. 21, 1914	100	5,100,000	6600	49.8	45.7	3.8	0.5	0.2
VIII	Aug. 25, 1914	100	5,600,000	6000	59.2	33.7	2.6	4.2	0.3
	Aug. 31, 1914	100	5,400,000	7800	52.4	39.3	4.8	3.0	0.5
IX	Feb. 13, 1915	...	.....	8000	51.0	45.0	3.0	1.0	
Control A	Aug. 27, 1914	100	5,500,000	8400	67.6	28.5	2.9	1.0	
Control B	Jan. 7, 1915	72	4,112,000	8800	67.5	26.0	6.0	0.25	0.25

Although the changes are not striking in all instances in Cases I and VII the findings correspond with those above mentioned. In the other cases the changes are less marked, though suggestive. Case IV (just returned from a vacation away from radium exposure) and control Case A under similar confining laboratory conditions, but not engaged in routine handling of radium, do not show such blood changes. Case IV at a later time showed an increase in lymphocytes.

Determination of Sensory Threshold. Although the sensory changes in the affected fingers, as above described, were marked, it seemed desirable to check these up by a determination of the "sensory threshold" of the affected compared with the unaffected fingers. These determinations were kindly made by Mr. John P. Richards under the supervision and direction of Professor E. G. Martin who devised special electrodes for the

finger tips for use with the Martin apparatus which has been previously described.[1] Dr. Martin reported that of the cases studied (Cases I, II, III, IV, and VIII) all except Case VIII, who was quite insensitive on all fingers, showed rather striking differences between the radiated and normal fingers—the former being much more insensitive. This relative insensitiveness to the faradic current might suggest injury to the nerve rather than to the terminal sensory end organs. It may, however, be due in some cases to increased resistance of the skin because of thickening of the horny layer.

With the idea of determining whether demonstrable histological changes occurred in the chronically affected and relatively insensitive finger tips, on October 7, 1914, under aseptic precautions, without anesthesia, fragments of skin, including a portion of the corium, were excised with scissors from the tip of the right forefinger and little finger of Case I; in the first instance there was very slight bleeding and little pain, while in the latter there was rather marked bleeding, soaking through a dressing, and considerable pain. The fragments were potted in Zenker's fluid. Both finger tips healed readily in a few days. Paraffin sections stained in eosin and methylene-blue showed numerous nerves and terminal special sense organs. No marked difference was evident between the fragment from the control fingers by this technic and specimens were not available for Weigert and Marchi methods.

Various methods have been devised, particularly by Dr. W. T. Bovie for avoiding these injurious local effects by the least possible contact of the fingers with the radium. Forceps or special vises are used for holding tubes and screwing in or out the tips and eyes; special applicators in the form of metal boxes have been constructed so that the active tubes may be added after the filtration and protection have been arranged, and the surface applicator is then slipped by forceps into a special rubber envelope and fastened with adhesive. This is particularly to avoid wrapping them up by hand in sheet rubber. Leaded gloves, fingers, etc., are clumsy and are not readily worn.

[1] Martin, E. G., Measurement of Induction Shock, New York, 1912.

In placing active tubes in special applicators it will probably not be possible to avoid all contact with radium and as the effects are not apparent at once as when handling very hot objects such as heated glass, but only after a period of days or even weeks, it will be difficult to train a worker to avoid all contact with the active apparatus.

In the work of making routine applications of radium there should be a rotation in the staff and persons affected should be freed at least temporarily from such work.

In order to avoid possible general disturbance the body should be protected as far as possible by metal screens in form of boxes or plates about the radium; there should be frequent ventilation of work rooms, particularly if there is radium emanation present, and a change of duty, shorter hours and periodic physical examination of those working with radio-active substances, with special reference to the blood examination, is indicated.

Summary and Conclusions. From the above it is evident that marked changes may occur on the fingers of those engaged in routine work with radio-active substances. These local objective changes consist chiefly of flattening of the characteristic ridges, thickening and scaling of the superficial layers of the skin and even atrophy and intractable ulceration. These lesions are usually slight compared with the marked subjective symptoms, such as paresthesia, anesthesia of varying degree, tenderness, throbbing and even pain. The persistence of such effects is noteworthy.

Various general systemic symptoms and also blood changes may be produced by exposure to radio-active substances. To avoid such local and general disturbance special protective and preventive measures have been devised, and those engaged in routine handling of radio-active substances are particularly cautioned.

To those above referred to who have aided me in this paper by descriptions of injuries, by blood examinations, finger prints or measurements of sensory threshold, I would again express my appreciation.

STREPTOCOCCUS BACTEREMIA IN ENDOCARDITIS

ITS PRESENCE BEFORE AND DURING THE DEVELOPMENT OF ENDOCARDIAL SIGNS[1]

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(By Invitation)

The frequent occurrence of a bacteremia has long been suspected in certain cases in which blood cultures have always been negative. One has often felt that our blood culture methods were very imperfect, that we failed to grow an organism when one was present. Rosenow's[2] methods are a decided advance and have placed in our hands means of investigating a large variety of diseases from which may come findings that will change present views of common diseases. The importance and wide range of the pathogenic influence of streptococci will become generally better appreciated and the association of certain diseases formerly often observed is even now being placed on a definite bacteriologic foundation.

In the heart clinic recently established at the Toronto General Hospital, in connection with the general medical outpatient clinic, it was felt that blood culture methods similar to Rosenow's might well be applied to the investigation of cases of suspected endocarditis since this affection is so often observed in those who have

[1] From the Department of Bacteriology and Department of Medicine, University of Toronto.

[2] The Newer Bacteriology of Various Infections as Determined by Special Methods, Jour. Amer. Med. Assn., September 12, 1914, p. 903.

never had rheumatism. It would appear reasonable that all cases of endocarditis are bacterial in origin, that the organism must be present in the blood for long periods at a time and could be demonstrated if our cultural methods were sufficiently perfected.

There was attending the medical outpatient department during the summer of 1914, a girl (the patient in Case 1), whose case had been diagnosed previously in Ward G, as one of pulmonary tuberculosis. However, she had no cough or signs of activity and her morning pulse rate was too slow. Yet she had slight fever, the temperature reaching 99° to 99.4° on an average about twice a week. There was then no murmur present. It was this case that suggested the great value of an efficient blood culture. Success along this line has been attained even beyond expectations, so that now cases formerly diagnosed as cases of chlorosis, anemias, indefinite attacks of fever, obscure tuberculosis and especially "nervous breakdowns" are being called endocarditis.

In this method we have a means, second to none other, of diagnosing this interesting and important disease. Indeed in a few cases it has been the only evidence obtained. A bacteremia has been obtained before the onset of the murmur or thrill and in the presence of a normal temperature. Still this technic is not all-sufficient. A culture was taken in a case of endocarditis and general acute serositis following inflammatory rheumatism three or four weeks before death. The culture remained sterile and at necropsy streptococci were cultured from the heart's blood and were even found in direct smears from the spleen. Still, positive cultures have been obtained when scarcely suspected and in rather more than half of the cases investigated.

This communication is a preliminary report of the presence of a non-hemolytic streptococcus, usually, though not always, producing green on blood agar, in the blood in some twenty-six cases of endocarditis investigated by a modification of Rosenow's culture methods during the past six months. The first twenty-three histories are pointed out for special consideration, as most of them represent a class of very mild endocarditis from which it is thought that positive blood cultures have hitherto not been obtained. The last three are added chiefly for comparison as they conform to the variety

commonly called in the literature "subacute bacterial endocarditis." Owing to lack of time and the depletion of the staff of the bacteriologic and pathologic departments by the war, in only a small percentage of suspected cases could cultures be made. Seven of the cases were found amoug the private patients of one of us (J. A. O.) in course of a small general practice in six months. At least as many others have been encountered in the same time in which cultures were not taken for reasons of age or convenience. During the same time only two cases of rheumatic fever have been treated in private practice and the three last cases (24, 25 and 26) are all that have been recognized of subacute bacterial endocarditis of literature type during the same or longer time in both hospital and private practice. If the figures are at all representative, the incidence of a mild form of endocarditis, of the type to be described, must be far greater than the so-called rheumatic endocarditis, or the subacute bacterial (Streptococcus viridans) form. The relationship between these varieties remains to be determined.

In April, 1914, Simons[1] published a critical review of bacterial endocarditis of all forms, summing up very well indeed present-day ideas of this disease. He defines it as those cases (1) which are either acute or chronic, (2) are associated with the presence of bacteria in the valvular lesion and (3) in the cirulating blood for some (usually a considerable) period of time and (4) are usually of fatal outcome. The idea is current that if organisms are present in the blood, especially in sufficient numbers to be recovered by culture, the case will end fatally in from a few weeks to two years. Simon uses the term bacterial endocarditis to include all organisms (except spirochetes). In this article, however, it is restricted to the type of case so well described by Osler,[2] Libman,[3] Schottmüller[4] and others, under such names as subacute infective or subacute bacterial endocarditis, endocarditis lenta, etc., and caused by a streptotoccus variously named Streptococcus viridans or mitis (Schottmüller), the endocarditis coccus (Libman), modified pneu-

[1] Critical Review, Bacterial Endocarditis, Quart. Jour. Med., 1914, xxii, 291.
[2] Chronic Infectious Endocarditis, Quart. Jour. Med., 1908–1909, ii, 219.
[3] The Etiology of Subacute Infective Endocarditis, Amer. Jour. Med. Sci., 1910, New Series, cxi, 516.
[4] Endocarditis Lenta, München. med. Wchnschr., 1910, lvii, 617.

mococcus (Rosenow), saprophytic streptococcus (Horder), and others. It is generally accepted that these terms all apply to the same organism now usually called the Streptococcus viridans though it must be remembered that this term includes a variety of strains of all grades of virulence and having special "affinities" for many different tissues.

Recoveries from the type of S. viridans endocarditis described above are very rare but do occur. All recoveries reported can be counted on the fingers. Now if every case of endocardial inflammation (that is, the so-called simple endocarditis, not including the arteriosclerotic form) be bacterial in origin, then all Simon's conditions characterizing bacterial endocarditis should be fulfilled except the fourth. It is certainly safe to predict that all of these twenty-three cases are not going to end fatally in two or even twenty years. It is a well-recognized clinical fact that simple endocarditis can heal and remain healed for a lifetime.

Characteristic symptoms and signs of "subacute bacterial endocarditis" are malaise, fever of all grades, chills, progressive emaciation, weakness and anemia, hematuria, petechiæ and other signs of embolism (hemiplegia, etc.), sweats, pigmentation, enlarged spleen and a terminal leukocytosis. Cases 24, 25 and 26 are types of this form of the disease, J. H. (Case 24) dying of emaciation, weakness and anemia, another patient (Case 25) of hemiplegia and one (Case 26) of embolism of the mesenteric artery, followed by gangrene of the small intestine, perforation, and peritonitis. The majority of the main series (Cases 1 to 23), have shown very few of the preceding symptoms (some none), but some have shown just enough to suggest that they might be mild forms (Case 1 especially) and that there is a gradation in severity from the mildest (Cases 15, 7 and 8) to the severest case (Case 1) in which there is anemia, joint pains, and considerable fever. Case 4 shows continual fever, nephritis and slightly enlarged spleen. None of the series is characterized by *progressive* emaciation, weakness, and anemia. What anemia and weakness has existed has not progressed, indeed has improved, though of course the time of observation has been short. The patient in Case 1 has been under observation one year. Most of the patients look perfectly well, feel well and had no anemia.

Hemoglobin below 60 per cent. was found in three cases. Six patients had no fever when the blood culture was obtained or while under observation, except a slight rise for a few days following removal of tonsils. The characteristic temperature appears to be an irregular one, normal all day, often for some days at a time, yet reaching 99° or 99.5° two or three days a week at irregular times of the day. To detect this the temperature must be taken systematically for considerable periods of time.

In seventeen cases the diagnosis was obscure, and was cleared up by the culture. In two or three, tuberculosis was suspected and may be present. T. D. (Case 9) conformed to the textbook description of chlorosis. Some suggested gastric ulcer. Two patients had symptoms somewhat similar to those in mild cases of typhoid (G. F., Case 11, and Mrs. H., Case 16). In fact both had suspicious Widal reactions and G. F. had an enlarged spleen and erythematous spots on the abdomen. But neither had the prostration, coated tongue, or malaise of typhoid and were ill too short a period of time. E. K. (Case 4) had symptoms of meningitis. But the most characteristic group was that made up of "neurasthenics." Nine complained of fatigue, weakness, depression, irritability, restlessness, crying attacks, etc. "Nervous breakdowns" were common. The preponderance of young adult females in the series was striking. Five were males and eighteen females. Seventeen were between the ages of sixteen and forty-one years. Now, when one is consulted by a neurasthenic, the temperature is taken carefully for two weeks, and if fever be present in the slightest degree, or even in the absence of fever, if a history of tonsillitis is obtained, and diseased tonsils and endocardial signs found, a blood culture is taken. Some seventeen neurasthenics have been investigated and a positive culture obtained in nine cases. Seventeen had no cardiac complaint or symptoms when first seen. Eight had, or developed while under observation, a precordial pain, radiating to the left shoulder and down the arm, usually associated with dyspnea and brought on by exertion. This anginal pain in many cases was apparently quite out of proportion to the physical findings and often associated with cutaneous hyperesthesia. Tonsillitis was the usual precursor. In the children (Cases 2, 11 and

22) it was the continuance of the fever after tonsillitis that suggested endocarditis. One waited three or four weeks after the acute attack of tonsillitis before the culture was taken.

A history of tonsillitis occurring in other members of the family was noted in ten cases. In the case of R. F. and G. F., brothers, the mother is subject to tonsillitis and was ill one year with "low fever" at nineteen. During the last winter the two boys, the mother and the nurse had, each, two or three attacks. In another family the spread of tonsillitis and associated diseases was remarkable. The mother, who has often had nervous breakdowns, had tonsillitis in December. Shortly afterward the husband had it also, followed in a month by appendicitis, and two or three weeks later, by a second attack with operation. While he was in the hospital the daughter, aged five, had tonsillitis, after which slight fever persisted for five or six weeks and a pulmonary and mitral systolic murmur developed for the first time. During this interval the baby had a sore throat. About the same time the nurse went home with tonsillitis. While she was away the other maid, the last member of the family, was taken ill with appendicitis and operated on. While she was convalescing the nurse, who had returned, had appendicitis also, with operation. While the little girl was ill with endocarditis the mother's sister came on a visit and two or three days after her arrival she too had an attack of tonsillitis. Several other members of the mother's family have had tonsillitis often, some with endocarditis.

L. M. (Case 7), is interesting, showing the relationship of tonsillitis, endocarditis, appendicitis, and gastric ulcer. Chronic appendicitis is blamed for causing gastric and duodenal ulcer. Possibly the real explanation is that both are results of the one infection. None of the series showed cholecystitis but two patieats had herpes zoster.

The mitral valve was affected in nearly every case; the aortic in only one or two. In three cases endocarditis was suspected, before the murmur developed. In two the culture was obtained before any murmur could be heard and in two others the only murmur present when the culture was obtained was a faint systolic heard in the second left interspace over the border of the heart.

There is some reason for thinking that this pulmonary systolic murmur is very often, more often than is thought, a transmitted mitral murmur, heard over the left auricular appendix. In most cases of mitral regurgitation, when looking at the cardiac action with a good screen, one can see a quick systolic dilatation in the left heart-vessel angle, which suggests a left auricular appendix being dilated with regurgitating blood. This has been seen when only a pulmonary systolic murmur could be heard on auscultation. In three or four cases in which opportunity has been had for watching the developmeat of mitral regurgitation the murmur was first heard in the pulmonary area and later (a few weeks, or in the case of Patient 1 nearly two months) in the mitral area. Moreover, in many cases of mitral incompetency a louder murmur is heard in the pulmonary area, or the space below it than at the apex; and in all cases of mitral regurgitation, observed recently, a pulmonary systolic was present as well as the mitral.

In only one or two of the series was any cardiac enlargement present and that not at all extreme (most in Cases 21 and 6). Four patients had a leukocytosis of short duration (Cases 1, 6, 14 and 19). Six showed signs of nephritis. Five had gastric symptoms. These are often very troublesome and difficult to explain. One had painful subcutaneous nodules on the hands. None had petechial hemorrhages.

Should the presence of the bacteremia alter the prognosis? Probably not, for we have learned from clinical experience that most of these patients get better and live many years. Most of them were too slightly ill to ordinarily be kept in bed. The prognosis of Patients 1 and 21 is uncertain. The latter has a severe anemia and syphilis. Next to these the cases of chronic endocarditis following rheumatism and chorea are most serious (Cases 6, 12, 13 and 14). Patient 6 is a small girl with a fairly well-advanced mitral stenosis. Still, even she should live longer than the two or even three and a half years allotted to the previously recognized cases of subacute bacterial endocarditis.

In treating them, at first in every case the patient was put to bed, with the idea that every one with an active endocarditis should be at rest. Most of the "nervous" patients improved rapidly while

in bed, but six did not show much change. Of these six, four have shown improvement since being allowed to be up and about, especially in Cases 3, 10 and 11. E. J. (Case 1) got up against advice and she became no worse. In fact she has lower fever now than she has had for six months. She is the most ill of the series. Hers would be classed as a type of mild case of the subacute bacterial endocarditis of the literature. Eight patients have had their tonsils out while under observation. Of these one (Case 9) improved afterward. Cases 2 and 10 were uninfluenced. Cases 16 and 22 have been too recent to draw conclusions. The other three patients were so slightly ill before the operation that no difference in symptoms was noted.

The patients were kept in the fresh air as much as possible, encouraged to eat and given iron. Quinin appeared to give benefit in one case. Autogenous vaccines were administered in seven cases. Large doses were worked up to, usually without reaction. Recently it has been customary to start with 500 million streptococci at the first dose and 1000 million at the second in the effort to obtain a reaction. Two patients with these doses had local reactions (Cases 1 and 5). It is difficult to see any difference in the course of those cases in which the patients were given vaccines, and those in which they were not.

The organisms recovered in the cases cited in this paper are being studied both as to their reactions and by animal experimentation. A detailed report of the results will be given at a later date.

Conclusions. 1. A streptococcus bacteremia is present in the great majority of cases of active endocarditis and probably in all in some stage of the disease.

2. Endocarditis more commonly follows tonsillitis in children and young adult females than is generally believed. Possibly this accounts for the frequency of mitral stenosis in females.

3. This low grade of streptococcic endocarditis is much more common than the so-called rheumatic endocarditis.

4. A large number of persons showing symptoms of the neurasthenic type are really suffering from a subacute streptococcic endocarditis.

5. Endocarditis may be active for considerable periods of time without symptoms.

6. A family incidence of tonsillitis and endocarditis (also appendicitis, gastric ulcer and other diseases which are often of streptococcic origin) is of frequent occurrence.

7. The pulmonary systolic murmurs so frequently found in "run-down" and anemic individuals are rarely functional.

On the other hand they usually indicate mitral regurgitation.

Special appreciation must be expressed to Dr. Goldie for referring several cases for study and for suggesting the role played by endocarditis in producing neurasthenic symptoms; also to Professor McPhedran and Dr. Clarke, Superintendent of the hospital, for facilitating observation of the cases in the wards.

Report of Cases

Case I.—E. J., aged twenty-two years, was admitted to Ward G, Toronto General Hospital, June 2, 1914, complaining of general weakness and backache for seven months with dizziness, fainting, dyspnea, and palpitation. Her family history is negative. She has had measles, mumps and chickenpox and has been anemic since seventeen. Two years ago she was confined to bed three weeks with fleeting pains in many joints without tenderness or swelling. The doctor diagnosed grip or muscular rheumatism. From Christmas, 1913, she lost thirty pounds in weight; had morning cough and expectoration, with pains in various joints and throughout the chest till the time of admission. Examination showed some dulness with bronchovesicular breathing found over right apex with no rales. The heart was normal in size, sound, clear and distinct. No murmurs. The tonsils were found diseased and removed in July, 1914. On admission, the blood count showed red blood cells, 2,500,000; hemoglobin, 58 per cent.; white blood cells, 8000. Urine normal. When discharged, July 28, the count showed red blood cells, 3,700,000; hemoglobin, 75 per cent. Her condition was much improved. While in the hospital the patient's temperature went above 99° five times in fifty-two days and reached 99° on seven other days. The pulse averaged from 70 to 80. The patient attended the outpatient department till December 8. During this time the temperature continued as described above. The pulse was slow in the morning—50 to 60—going to 90 and 100 in the afternoons. During August a systolic thrill in the mitral area was detected. In September a precodial pain developed, brought on by exertion and associated with dyspnea. At the same time there was a suspicion of a pulmonary systolic

murmur. On December 8 the patient was readmitted to the hospital (on account of angina pain and a slight swelling of the feet) for a rest. At this time the heart was not enlarged and the presence of a mitral systolic murmur was questioned. A pulmonary systolic murmur on exertion could be heard. On December 18 her temperature rose to 100.5° and from then till now (June, 1915) her temperature has oscillated from 97° to 102°, reaching the high point at irregular intervals, sometimes A.M., sometimes P.M. There has been no cough since June, 1914. The pulmonary condition is unchanged. The murmurs are becoming rougher. December 24, blood culture taken by Rosenow's method showed Streptococcus viridans on the second day. January 13, the mitral murmur was loud and rough with a rougher pulmonary systolic murmur and accentuated pulmonary second sound. Red blood cells, 3,920,000; hemoglobin, 65 or 70 per cent.; white blood cells, 9000; polymorphonuclears, 72 per cent. The urine showed a few granular and hyaline casts. Spleen and liver were not enlarged. The patient remained in bed three and one-half months with no improvement. Since April 1, she has been going about with her condition unchanged except the temperature does not go quite so high. She has been given autogenous vaccine (500,000,000 per dose) which gave a local reaction about two inches in diameter but which has not altered her condition.

CASE II.—R. F., a boy aged five years and nine months, was seen on February 15, 1915, complaining of feverishness continuing after tonsillitis. His mother often has severe tonsillitis and had endocarditis for one year at nineteen. Brother has subacute Streptococcus viridans endocarditis. Had an attack of feverishness without evident cause in 1912 and again in November, 1913. Examination showed a bright boy, slightly pale, restless, constantly moving. The organs were normal except the heart, which showed a systolic thrill and murmur in the mitral and pulmonary areas. On March 9 a blood culture showed S. viridans. The urine showed a small amount of albumin and granular and hyaline casts. Red blood cells, 4,500,000; white blood cells, 7500; hemoglobin, 80 per cent. For the past four months his temperature has averaged slightly above 99°, reaching 99.8° or 100° two or three times a week. He was given eight or ten doses of autogenous vaccine, beginning with 25,000,000 and increasing to 400,000,000 with no appreciable effect on the course of the disease. April 24, his tonsils were removed, cultures from which gave Streptococcus viridans. The boy has been in bed four months during which time he has grown and improved in general appearance. He now looks and feels perfectly well, yet the fever continues unchanged. His mitral murmur has become fainter.

CASE III.—C. M., aged forty-one years, a nurse, was admitted to the Toronto General Hospital, February 14, 1915, complaining of fatigue, nervousness, general pains in limbs and back, coccygodynia, palpitation

of the heart and slight dyspnea on one or two occasions. Her right knee was swollen for two or three days. She had had no previous illnesses except repeated "nervous breakdowns." Was off work four months in 1913 for coccygodynia and a nervous breakdown. Family history negative. The patient was a well-developed, well-nourished woman with all organs normal except the heart, which showed mitral and pulmonary systolic murmurs, without cardiac enlargement. Pulse averaged 70 to 80. The temperature reached 99° nearly every day and on four occasions reached 99.5° between February 14 and April 28. Red blood cells, 5,000,000; white blood cells, 8700; hemoglobin, 75 per cent.; polymorphonuclears, 72 per cent.; systolic blood-pressure, 115; diastolic, 78. The urine, specific gravity 1.015, showed a trace of albumin and red cells on one occasion and always a few granular and hyaline casts. On February 14, a Rosenow blood-culture showed Streptococcus viridans. An autogenous vaccine was given up to 700,000,000 per dose with no reaction or appreciable effect. Patient remained in bed for two months without change. She was then allowed to be up and to walk about. Her temperature ran higher for two or three weeks, then became normal and has remained so with a corresponding improvement in symptoms.

Case IV.—E. K., a nurse, aged twenty-one years, entered the hospital February 19, 1915, complaining of severe pain in the lumbar region and in the front of thighs. Six weeks previously she was in bed three days with tonsillitis accompanied by an urticarial rash. Three days before admission pain began in her thighs and two days later in her back; it was severe enough to prevent sleep and require three-fourths grain of morphin a day. Family history negative. She had no previous illness except tonsillitis. Heart, lungs, liver and spleen were normal. No retraction of the head or Kernig's sign. Reflexes normal. Sensation normal. On February 22, a lumbar puncture was done and an antimeningococcus serum given as there were several cases of meningitis in the hospital at that time. The fluid was clear, cell count 4 or 5.

February 23. Her condition was unchanged. A second lumbar picture showed a turbid fluid. A slight hemorrhage prevented an accurate cell count but the fluid which came last contained many polymorphonuclear leukocytes, lymphocytes, and endothelioid cells. A smear showed numerous gram-positive diplococci. On account of the absence of other signs of meningitis and the localized nature of the pain, the cord condition was considered focal and possibly embolic, though no cardiac murmur was present. Two days later a blood-culture was taken which showed a gram-positive coccus growing in pairs and short chains, which on further culture proved to be Streptococcus viridans.

March 1. A dark brown pigmentation in the form of a coarse network developed on the inner side of the thighs. The pigmentation corresponded

to the purple mottling which occurs on the arms and legs in vasomotor disturbances. This pigmentation has persisted for nearly three months. March 7, the pulmonary second sound was noted accentuated and a very faint systolic murmur was heard in the pulmonary area. She constantly moved about in bed.

March 25. Pains in the thighs have continued till now. A soft pulmonary systolic murmur is still heard.

March 31. Some pains are still present in the knees and thighs.

April 2. A systolic murmur is heard in the mitral area.

April 12. The patient is feeling fine, the mitral systolic murmur is becoming louder.

May 10. The heart condition is unchanged. Patient is feeling perfectly well.

May 23. The patient began to sit up.

June 18. Patient can go upstairs with very slight increase in the rate of the heart's action, with the rate returning to normal in less than a minute on lying down. During the first ten days of this period the temperature remained above 99°, reaching on one occasion 101.5° usually going from 99° to 100° daily. From March 1 to the time of discharge on June 19, the temperature has reached 99.4° on fifteen occasions. At periods it remained below 99° for a week at a time. The urine contained a trace of albumin and red blood cells on two occasions. White blood cells, 12,000 on admission, were found 8000 in a week and remained from 8000 to 9000. Red blood cells, 4,200,000 on admission. When the patient was discharged, red blood cells, 5,200,000; hemoglobin, 74 per cent.; systolic blood-pressure, 104; diastolic, 84. On June 1, a second blood culture was positive in both aërobic and anaërobic cultures.

Case V.—Dr. M., aged twenty-five years, entered the hospital on March 12, for tonsillectomy. He had had tonsillitis five or six weeks before, which was followed by pains over the tendons of his legs and his ankles. He had rheumatic fever at the age of nine, and was ill several weeks. He had rheumatic fever at fourteen, and was in bed three weeks. He had tonsillitis frequently every year. His father had rheumatism. The patient was well nourished, well developed, did not appear ill, the heart was not enlarged. Systolic murmur in the mitral and pulmonary areas; was heard best in the pulmonary area. For two or three weeks following the operation there was arthritis in the wrists and shoulders. He had secondary hemorrhage from one tonsil on March 21. March 26, an aërobic blood culture was sterile. April 5, (three weeks after operation) an anaërobic blood culture gave hundreds of colonies of Streptococcus viridans. On May 25 both anaërobic and aërobic blood cultures were negative. Red blood cells, 5,500,000; white blood cells, 9000; hemoglobin, 80 per cent. Urine negative. He was given six doses of autogenous vaccine—the first 500,000,000

streptococcus, the second and others 1,000,000,000. These produced local reactions. From time to time the murmur varied in intensity, becoming louder and rougher and then softer and fainter. He was discharged on June 5.

During all of this time his temperature was normal with the exception of two days following the operation when it reached 99.5° and 100° respectively.

Case VI.—Miss B, aged eight and one-half years, weighed three and one-half pounds at birth. At two and one-half years she had adenoids and otitis media. The adenoids were removed. The heart was normal. In June, 1912, she began to be restless at night with night terrors, which lasted six weeks. Then she began to have nausea and pallor in the mornings with no elevation of temperature. On the fourth day her heart was said to be badly diseased. After three weeks there was marked muscular twitching and loss of voice, said to be chorea. She was confined to bed until the end of October. All of this time no record of temperature was kept. In the beginning of November she was allowed to be up and in December the doctor said the heart was as well as ever it would be. In February, 1913, she contracted a catarrhal cold and looked very tired. The doctor found the pulse rate 145 and the heart violent and irregular in action with a low afternoon temperature. Twitching movements of muscles again appeared. In a period of improvement in March the tonsils were removed. She was confined to bed until June 5, but was not allowed to walk until September, at which time the heart was apparently normal in size and no murmur could be made out. In October, after strenuous exercise, a soft systolic murmur could be detected.

In December, 1913, she had a slight catarrhal cold. Between this and Easter, 1914, she had two colds with high temperature, but was only confined to bed for two or three days. The heart seemed unaffected. The child continued active and strong except in September, 1914, when abdominal tenderness led to a reëxamination and it was stated that no abnormal condition could be found in the heart. In November she was examined again for abdominal pain. At this time there was a slight systolic murmur. In February, 1915, she had a catarrhal cold, contracted from the mother, marked sore throat, glandular enlargement, high temperature, and a leukocytosis of 19,000.

The heart was dilated, very rapid, with a harsh presystolic and systolic murmur. In April a Rosenow blood culture gave a plentiful growth of Streptococcus viridans. Leukocyte count, 11,000. At this time quinin—3 grains four times a day—was administered. The temperature gradually fell to normal in about two weeks' time. Vaccine 1,000,000,000 increased to 2,500,000,000 every fourth day. Only once was there local reaction. The pulse rate ranged from 88 to 110. On June 10, the child was allowed

to get up. The pulse rate increased only 5 to 10 beats during the first three or four days, then remained about 100 until the present date. The child is up and playing about, six hours a day. At no time throughout the course has there been found any abnormal urinary secretion.

Case VII.—L. M., aged twenty-four years, a nurse girl, entered Ward G for investigation of symptoms of indigestion consisting of heartburn and nausea. She also complained of weakness and fatigue. Her mother died of heart disease at thirty-seven. The patient's tonsils were removed (incompletely ?) ten years ago. She had appendicitis with operation six years ago; tonsillitis two years and one month ago; two attacks of gastric ulcer twelve and nine months ago. Has vomited "coffee grounds." The organs are normal except the heart, which shows a rough mitral and pulmonary systolic murmur with no cardiac enlargement. The tonsils were badly diseased. Red blood cells, 4,800,000; white blood cells, 8000; hemoglobin, 75 per cent. Urine normal. Test meal and bismuth meal revealed nothing abnormal. Tonsils were removed May 23, and showed marked disease. Cultures from the tonsils and the Rosenow blood culture showed Streptococcus viridans. The temperature reached 99° occasionally. The patient felt perfectly well after a week's rest in bed.

Case VIII.—E. B., aged twenty-five years, a music teacher, was referred from Dr. L. on April 23, 1915, for investigation, on account of two attacks of iritis lasting three weeks. She complained of being run down, tiring easily, headaches, and some depression. Has had headache over the right eye all her life. She was operated on for fibro-adenoma five years ago and hernia eight years ago. One month ago she had tonsillitis. Her sister is subject to tonsillitis. The mother died of appendicitis. On examination the patient, a well-nourished woman, did not appear ill. The heart showed no enlargement or thrill. There were systolic murmurs in the mitral, pulmonary, and aortic areas. Spleen slightly enlarged by percussion, not palpable. Other organs normal. Red blood cells, 4,900,000; white blood cells, 6600; hemoglobin, 85 to 90 per cent. Crypts of the tonsils contained an exudate. The temperature was normal. A blood culture on April 28, showed profuse growth of streptococcus. The tonsils were removed May 31. Cultures from the tonsils showed a similar strain of Streptococcus viridans to that obtained by blood culture. After six weeks' rest she feels perfectly well. Her temperature continues normal.

Case IX.—T. D., a nurse girl, aged twenty-one years, was admitted November 9, 1914, to Ward G, Toronto General Hospital, complaining of symptoms of indigestion. The patient also had palpitation, dyspnea, dizziness, and pain in the legs. One brother died of appendicitis. She had had measles, whooping cough and growing pains as a child and was in bed one week three years ago with "muscular rheumatism." She had had tonsillitis often. She was a well-developed, well-nourished girl with pallor

of skin and mucous membranes. She had several decayed teeth and the tonsils showed exudate in the crypts. The lungs were normal, the heart also normal in size. A soft pulmonary systolic murmur was heard with accentuated pulmonary second sound. On admission, red blood cells, 4,700,000; hemoglobin, 50 to 60 per cent.; white blood cells, 6800; polymorphonuclears, 69 per cent. On discharge, red blood cells, 5,150,000; hemoglobin, 72 per cent. The urine on one occasion showed a trace of albumin. The temperature reached 100° daily, till December 18, when the patient's tonsils were removed. After the operation, for eleven days her temperature reached 101° daily. From December 30, her temperature reached 99° or slightly over nearly every day, but gradually improved until at the time of her discharge, on March 26, it had remained below 99° for nineteen days, with the exception of one day when it reached 99.5°. On January 4, a Rosenow blood culture showed a streptococcus growing in short chains and clumps. During the last week of her stay in the hospital two Rosenow blood cultures were sterile. At intervals a systolic murmur was heard in mitral, pulmonary and aortic areas and some days its presence was questioned. Exercise increased intensity of the murmur. The screen examination showed a systolic pulsation in the region of the left auricle with no enlargement.

Case X.—E. B., aged twenty-four years, a nurse, entered the hospital January 27, complaining of weakness, nervousness, depression, palpitation of the heart, shortness of breath and precordial pain on slight exertion, at intervals, for four years, which had become worse during the last four months. Her brother had a severe endocarditis four years ago with recovery. The patient had had tonsillitis several times. Four years ago she had an infected finger which was several weeks in healing, followed by scarlet fever and diphtheria. She had not felt well since and frequently had attacks of nausea and vomiting. Before entering the hospital the patient had been in bed nearly two months for the above complaints with slight fever nearly every day. On examination the patient, a well-developed, well-nourished woman, does not appear ill but is very restless. The movements almost suggest chorea. All the organs are normal except the heart. A systolic murmur is heard in all areas. The pulmonary second sound is accentuated. The heart outline shows slight bulging to the left at the base. Red blood cells, 4,500,000; white blood cells, 9000; hemoglobin, 67 per cent. on admission, had increased to 78 per cent.; systolic blood-pressure, 125; diastolic, 70; polymorphonuclears, 73 per cent. The urine has never contained albumin but hyaline and granular casts are present occasionally. Her temperature at first reached 99° or over one or two days a week but was 99° only once during the last three weeks of her stay in the hospital. The blood culture taken before admission showed a streptococcus and Staphylococcus albus, the latter no doubt being a skin contamination.

A second blood culture remained sterile, a third and fourth were positive, showing a streptococcus which coagulated serum but did not produce green. A similar streptococcus was obtained from her tonsils, which were removed on March 27. The patient was kept in bed three months during which time she was greatly troubled with precordial pain and headaches. Since being allowed up her general condition has improved and she has had less fever.

Case XI.—G. F., a boy aged fourteen years, was seen January 27, 1915, complaining of incomplete recovery from tonsillitis. The patient is a brother of R. F. His past illnesses were chickenpox and scarlet fever at seven—average attacks without complication—and he has had indefinite attacks of fever all his life. In November, 1914, at the same time that his brother was having a feverish attack, this boy was feverish for three weeks and had erythematous spots about half the size of typhoid spots, spread profusely over his abdomen. The spleen had enlarged. A Widal test showed agglutination in half an hour with a 1 to 40 dilution but not complete agglutination or loss of motility in one hour. His temperature reached 103° and came down by lysis, but there was no prostration. His tongue was clean and he felt quite well except that he tired very easily. A mitral systolic murmur was heard. February 8, his heart was 11.5 cm. in transverse diameter, fourth space and well rounded. There was a systolic thrill and murmur and a rough first sound in the mitral area with an accentuated pulmonary second sound. The systolic murmur was also heard in the pulmonary and aortic areas. The murmurs increased on exertion. His spleen continued enlarged one or two finger breadths below the costal margin for three or four months following his November illness. The liver was 3 cm. below the costal margin. Red blood cells, 5,000,000; white blood cells, 8000; hemoglobin, 90 per cent. Urine normal. His temperature was irregular, being normal about half of the time reaching 99° or 99.5° two or three times a week. His pulse averaged about 100. He has been in bed four months. Autogenous vaccines were used in increasing doses, from 50,000,000 to 1,500,000,000, without reaction.

April 1. The spleen is not palpable and the thrill has nearly disappeared. April 24 the tonsils were removed. Now (June 16) he has been sitting up for three weeks; during this time his temperature range has been nearly normal. It has been below 99° for the past week. Since going about, his pulse has slowed to from 76 to 80. A similar organism was recovered from his tonsils as from the blood, producing brown on blood agar.

Case XII.—M. M., a schoolgirl, aged seventeen years, entered Ward G, January 8, 1915, for an attack of chorea, which she had had at intervals for eight years. She had rheumatism at ten, scarlet fever, diphtheria and whooping cough at thirteen and tonsillitis at fourteen, after which her tonsils were removed. She was an impulsive, emotional, irritable girl.

This was her third admission for chorea. During her previous admissions she had mitral regurgitation with some extrasystoles. She had hyperesthesia and hyperalgesia over left half of chest which extended gradually to the arm, abdomen, and leg. On examination on January 8, she was found to have presystolic murmur and thrill with marked precordial pain and hyperesthesia over left half of chest. She cried when being percussed on the left side. Over this area she called the hot test tube "cold" and the cold one "hot." Her spleen and liver were not enlarged. Heart showed extrasystoles and short runs of tachycardia. Red blood cells, 5,000,000; hemoglobin, 60 per cent.; white blood cells, 7000; systolic blood-pressure, 120; diastolic, 75. Urine: no albumin or casts. January 12: Blood culture showed Streptococcus viridans. She had slight fever throughout her stay in the hospital and developed herpes zoster between the twelfth rib and iliac crest on the left side. She was discharged on May 3, improved.

Case XIII.—A. H., aged eighteen years, was admitted first on September 20, 1912, and again June 26, 1913. She was admitted the third time October 1, 1913, and then again January 26, 1914, complaining of tonsillitis, dyspnea, and weakness. On October 2, 1913, her tonsils were removed. No bacteriologic report is available. At that time her pulse was 92, going up to 120 on walking. She had attacks of palpitation. Her previous illnesses were measles, rheumatism in 1911, when she was in bed for six weeks. She had rheumatism also later in the same year, for three months, but was not in bed. She had tonsillitis several times a year. Systolic and diastolic murmurs were heard in all areas. There was a mitral presystolic murmur. Point of maximum intensity of the apex beat is in the fourth left interspace, two and one-half inches from the midline. Temperature rises to 99° occasionally. Pulse is about 100. Systolic blood-pressure, 110 to 130; diastolic, 80 to 70; red blood cells, 3,500,000 to 4,900,000; white blood cells, 5000 to 6000. Wassermann negative. Urine normal. This patient has been attending the outpatient department since 1912, with the exception of the times when she was admitted to the hospital. Rosenow blood culture was taken on January 13, 1915, positive at the end of a week for Streptococcus viridans.

Case XIV.—E. G., a schoolgirl, aged sixteen years, came to the outpatient department in January, 1915, complaining of dyspnea and precordial pain on exertion. One brother and sister had had rheumatism; the father died of pleurisy at forty-one. The patient had measles in 1904 scarlet fever in 1911, tonsillitis often. The tonsils were removed in 1912, the patient had diphtheria in 1913, chorea from March to August, 1914, with endocarditis. From January to March 9, 1915, she had slight fever, the temperature reaching 99.5° once or twice a week. On February 2 she had a presystolic thrill and murmur and systolic murmur in the mitral area. Temperature 99.6,° pulse 125. There was some twitching of the

shoulders and face. She was admitted to Ward G. March 9. The heart was 11.5 cm. wide in the fourth space by orthodiascope. Murmurs were the same as before. Over the apex of the right lung, anterior and posterior there was slight dulness with prolonged expiration and moist rales. The urine showed a trace of albumin on one occasion but it was not a catheter sample. Subsequent catheter specimens showed no albumin or casts. Red blood cells, 5,000,000; white blood cells, 11,000; hemoglobin, 80 per cent.; systolic blood-pressure, 120; diastolic, 75. No tubercle bacilli were found in the sputum. On May 13, streptococcus was found on blood culture. With rest in the hospital precordial pain and dyspnea disappeared and her general condition was improved, though at all times the patient appeared well. She had had no cough at any time while under observation. A screen examination showed no suspicious shadows in her lungs.

Case XV.—J. H., a factory hand, aged twenty-three years, was sent into Ward G, April 19, from the medical outpatient department with a provisional diagnosis of subacute streptococcus endocarditis. She complained of fatigue, depression and a gone feeling in the epigastrium coming on an hour after food and relieved by taking food. Her family history was negative. She had no previous illnesses except measles and chickenpox when a child. All the organs were normal except the heart, which showed a systolic murmur in all the areas, best heard in the pulmonary and aortic regions and up the vessels of the neck. There was no cardiac enlargement. A test meal and bismuth meal revealed nothing abnormal. Red blood cells, 400,000; hemoglobin, 85 per cent.; white blood cells 7600; systolic blood-pressure, 116; diastolic, 72. Wassermann negative. Urine examination revealed nothing abnormal. May 11, Rosenow blood culture showed profuse growth of Streptococcus viridans. During her twenty days in the hospital the temperature was over 99° five times and below 98° the last week. She was returned to the outpatient department for observation.

Case XVI.—Mrs. M. H., aged twenty-seven years, on June 15, 1915, complained of being miserable, easily tired, faint, giddy, "foolishly nervous," wishing to be alone and of a feeling of thickness in her throat. Her brother had frequent attacks of tonsillitis. She had tonsillitis three weeks ago and four or five times previously. In the spring of 1914, she had an attack of fever of indefinite cause, lasting seven or eight days. Three Widals were taken—two done in one laboratory were reported negative, and one in another was reported positive. She had pleurisy five years ago and pneumonia six years ago. She had mumps, measles, chickenpox, whooping cough and malaria (?) when a child. At twelve she was ill a week with fever and pain in the left shoulder. At thirteen she had suppuration around all her finger nails, successively, lasting throughout the winter. From June 15 to June 29, her temperature reached 99° or 100° every day.

On examination nothing was found abnormal except diseased tonsils and a slight thrill in the mitral area. On June 29 Streptococcus viridans was recovered by blood culture. On June 25 her tonsils were removed, cultures from which showed a similar streptococcus. Urine normal. Hemoglobin, 80 per cent.; red blood cells, 4,928,000; white blood cells, 8400.

Case XVII.—A. M., a housewife, aged forty-one years, was seen through the kindness of Dr. Shenstone. Entered the private ward pavilion, March 15, 1915, with enlargement of the cervical glands, one of which was removed for diagnosis and found to be tuberculous. On examination she was found to have a slight mitral regurgitation and painful subcutaneous erythematous nodules on the hands. White blood cells, 7200; hemoglobin, 65 per cent.; polymorphonuclears, 80 per cent. Urine normal. During her stay of two weeks in the hospital she had daily fever averaging about 100° but the temperature gradually approached normal. Subsequently her temperature remained normal. Streptococci were recovered from her blood by a Rosenow culture and a vaccine was made and administered after she left the hospital, that is, after her improvement. She is now apparently well.

Case XVIII.—C. H., a saleslady, aged nineteen years, was admitted to Ward G, on December 28, complaining of swelling and pain in the feet and ankles, with slight pain in the knees, elbows, wrists, abdomen and left side of the chest for six months. Has been short of breath since scarlet fever eleven years ago. Mother died three years ago of tumor in the chest; had had rheumatism. Two brothers died of tuberculosis. The patient had measles and scarlet fever at eight, severe tonsillitis at nine, at sixteen and several times since, middle-ear disease on both sides at ten, whooping cough at sixteen. At eighteen she had three teeth removed for diseased roots. On examination the patient was a well-developed, well-nourished girl with good color. Puffiness of the ankles and wrists was noted with purple vasomotor mottling on arms, hands, legs, and feet. Pains in the joints had been of very short duration with no tenderness or swelling. Heart was not enlarged. There was a faint systolic murmur in the mitral, pulmonary and aortic areas and superficial hyperesthesia over the precordial area. The other organs were normal. Urine normal. Red blood cells, 5,200,000; white blood cells, 8000 to 11,000; hemoglobin, 75 per cent. Systolic blood-pressure, 115; diastolic, 75. On March 26, Rosenow blood culture showed streptococcus. Her tonsils were removed on April 23, and culture showed a similar organism to that from the blood. From December 28 to the time when the blood culture was taken on March 23, her temperature reached 99° only twice. Since her tonsils were removed her temperature reaches 99.4° frequently. At times, however, it is below 99° for eight or nine days.

Case XIX.—Mrs. W., aged thirty years. Tuberculosis is of frequent occurrence in family. The patient was a healthy child and was in good

health until the age of twenty-seven. Then, after a period of hard work and long hours, she became nervous, lost weight, developed throat-clearing. She consulted her physician because of pain in the left chest. Examination revealed thickening of the upper left hilus. Sputum was negative for tubercle bacilli on several occasions. No changes could be made out in the lung tissue or the heart. The temperature, taken for a week, gave no abnormal rise nor was the pulse at any time above 88.° The tonsils showed a deposit in the crypts and there was no cervical gland enlargement. She rapidly recovered after four or five weeks' rest and remained well until January, 1915. At this time she had a catarrhal cold and remained in bed for a week but felt weak and tired for four or five weeks. She did not consult a physician until a fresh cold developed at the end of March. At this time precordial distress was frequent and heart action at times violent. A systolic murmur of varying intensity could be made out at different examinations. The Rosenow blood culture showed a sparse growth of Streptococcus viridans. After two weeks in bed the precordial distress had disappeared and the systolic murmur became soft, even and constant. At present the patient has increased in strength and color and claims to be perfectly well. Throughout she had no abnormal urinary signs. The leukocyte count varied from 17,000 down to normal from the beginning of the illness to the time she was up.

Case XX.—M. D., a governess, aged twenty-seven years, entered Ward G, for investigation for precordial pain going down the left arm and shortness of breath which came on a week after the tonsils had been removed. Four brothers and sisters have tonsillitis often, one brother had appendicitis. She had rheumatic fever twelve years ago, was in bed six weeks and out of school three months. Has been short of breath since, becoming worse the last two or three years. Three weeks ago she had tonsillitis, ten days ago her tonsils were removed. She is a well-developed, well-nourished woman, pulse 88, temperature never above 99° (has reached 99° three times in fifteen days). Her heart is not enlarged. There is a rough mitral and pulmonary systolic murmur with accentuated pulmonary second sound. Urine normal. Red blood cells, 4,800,000; white blood cells, 8200; hemoglobin, 75 per cent. Rosenow blood culture showed streptococcus.

Case XXI.—H. L., a laborer, aged thirty-nine years, admitted to Ward G, April 3, 1915, complaining of general weakness and precordial pain for three months. Family history negative. He had always been well and worked hard up to three months ago when he began to lose weight and strength and had frequent epistaxis. He noticed himself becoming pale. Then a pain developed over the precordium radiating to the shoulder and down the left arm, accompanied by dyspnea and brought on by exertion. On examination it was found he was a well-developed man, having no scars or lymphatic enlargement. His skin was yellow, and the mucous membranes

were very pale. Heart enlarged to left 12 cm. in the fifth space, apex beat in the fifth space 12 cm. out. The first sound was replaced by a systolic murmur in the mitral area, also heard all over the precordium. Superficial hyperesthesia exists over precordial area. Spleen reaches to the costal margin, the liver two finger breaths below costal margin. Reflexes normal. Red blood cells, 3,400,000; hemoglobin, from 25 to 30 per cent.; white blood cells, 7500; polymorphonuclears, 65 per cent.; lymphocytes, 25 per cent.; eosinophiles, 5 per cent.; basophiles, 5 per cent. Poikilocytosis—no nucleated red. Systolic blood-pressure 125; diastolic, 70. Urine 1.016, no albumin or deposits. Wassermann strongly positive. April 15, Rosenow's blood culture yielded a streptococcus. During his stay of seven weeks in the hospital the patient had irregular fever, going from 99.5° to 100,° and one occasion reaching 102° for three days. His pulse averaged 80. He was given injections of salicylate of mercury intramuscularly. His blood picture was unchanged when he was discharged.

Case XXII.—E. S., aged seven years, had tonsillitis, in April, 1915, following which the temperature remained elevated, reaching from 99.5° to 99.8° three or four times a week. A *bruit de diable* was heard under the right clavicle during the attack of tonsillitis with a mitral and pulmonary systolic murmur. The patient had streptococcus tonsillitis at nine months of age. She had an indefinite illness during January, 1915, with slight fever for three weeks. A mitral systolic murmur was heard then on one or two occasions but afterward disappeared. The tonsils were removed in May; the cultures showed Streptococcus viridans. On June 9, a blood culture also showed Streptococcus viridans. Slight fever is still present on this date (June 20) though she appears perfectly well.

Case XXIII.—Dr. Mc., aged thirty-six years, had arthritis in right knee in 1902 and was in bed eleven weeks. Since 1901 he has had pain and swelling over the outer side of the left foot in front of the os calcis. This has been gradually increasing. Röntgenograms show formation of spicules of bone. Now the foot is considerably swollen and two boggy points of swelling are situated on the outer part of the foot below and in front of the ankle. The skin is not discolored and there is no tenderness. The heart shows very faint systolic murmurs in the pulmonary and mitral areas; there is no enlargement. Hemoglobin, 95 per cent. The patient feels perfectly well and conducts a large practice. The swellings in the foot were aspirated and two or three drops of thick fluid obtained which on culture was sterile. A blood-culture taken on May 28 showed Streptococcus viridans.

Case XXIV.—J. W., aged thirty-three years, a traveler for agricultural implements, in May, 1914, had an attack of tonsillitis, in July a gonorrheal urethritis. The discharge lasted eight days and returned for

three or four weeks during August, when he noticed some arthritis in his left thumb with pains in the legs below his knees. He was given vaccines. After the fifth dose he developed chills which recurred every three or four days, this continuing for a month. Then he was given streptolytic serum and Neisser's mixed vaccine for suspected gonorrheal endocarditis. This was followed by an improvement of short duration.

During October and the first half of November, 1914, he had severe rigors daily, his temperature reached 105°, pulse 150 at times, with delirium and vomiting. He then improved again and when first seen, on December 14, his temperature had just reached normal, vomiting had ceased and he began to eat quite well. His pulse was 80. A dusky flush showed on his face. He was torpid and very depressed. He complained of pain to the right of the sternum and could not turn in bed. His heart was enlarged to the left and showed a systolic and diastolic murmur at the base with reduplication of the first and second sounds. The right lung posteriorly showed a small area of dulness near the inner border of the top half of the scapula with moist rales and slight bronchophony. The spleen and liver were not enlarged. Red blood cells, 5,000,000; white blood cells, 8000. A prostatic smear and culture showed no gonococci. The urine showed no albumin or casts.

His temperature continued normal from December 14 to January 1. December 18, an ordinary and Rosenow blood culture showed an organism which grew in pairs and short chains. A twenty-four hour agar slope injected intraperitoneally killed a mouse in thirty-nine hours. The organism was recovered from the peritoneal exudate, from the liver, and from the heart's blood. This organism was a gram-positive coccus, growing in pairs, and possessed a distinct capsule, staining with a methylene blue and fuchsin capsule stain, produced a green color on blood agar and lost its capsule on cultivation. On December 28, the second blood culture was positive. The patient was then feeling fine, was hungry, and was allowed to sit up to eat his meals. January 1, his temperature was 102°, with pericardial friction. He was given 100 c.c. of antipneumococcus serum daily for five doses, and had a slight serum rash three days after the last dose.

February 1. Chills have continued at irregular intervals with epigastric pain and vomiting. Blood culture again was positive. An autogenous vaccine was made and given in increasing doses from 25,000,000 to 600,000,000 at three-day intervals, without reaction.

February 8, a mitral systolic murmur was heard. Chills continued till March 15. The diastolic murmur was sometimes heard in the mitral areas. The character and intensity of the murmurs often changed.

April 18. The patient was given 0.3 grain neosalvarsan intravenously. Red blood cells, 3,900,000; white blood cells, 4000; hemoglobin, 40 per cent. The urine contained a few hyaline casts. Temperature was normal.

During May temperature remained normal, the patient becoming weaker. There was some general edema. Vomiting had ceased. He had taken more nourishment but was not gaining in strength.

June 1. Edema increased. Patient very emaciated.

June 8. Red blood cells, 2,100,000; white blood cells, 8500; pulse, 72. His temperature was subnormal. The urine contained no albumin or sugar, a few hyaline and granular casts. The patient died, but no necropsy was obtained. A blood culture taken from the right auricle half an hour after death remained sterile.

Case XXV.—E. B., a steamfitter, aged twenty-seven years, was brought to Ward G, on February 2, 1915, suffering from hemiplegia. December 20, 1914, the patient felt ill, becoming tired easily. January 5, he stopped work on account of general malaise and pain in the left knee. From January 5 to February 1, he was up and about the house but felt very ill some days, other days quite well. He was feverish at times and at other times chilly. He had some shortness of breath. February 2, he became gradually hemiplegic during the course of one hour. First he dropped a book, then he found he could not move his arm. Then, after lying down for an hour, he fell on attempting to walk. He found he could not move his leg. There was no pain or loss of consciousness. He had had rheumatism at fifteen. On examination, pulse was 95, temperature 103°. He lies in a stupor but answers when spoken to sharply. Lips and tongue are dry. The left side of the body and face is paralyzed, flaccid, and anesthetic. He could not see objects in the left visual field. The tongue deviated to the left. The superficial reflexes were absent on the left side. Deep reflexes were exaggerated with ankle clonus on the left side. There was loss of sphincter control.

Heart: Apex beat 10 cm. to the left, sharp and "flapping." Presystolic thrill and murmur in the mitral area with systolic murmur in the mitral and pulmonary areas. The lungs show signs of bronchopneumonia. The liver is not enlarged, the spleen not palpable. Red blood cells, 5,000,000; white blood cells, 22,000; polymorphonuclears, 82 per cent. Systolic blood-pressure 132; diastolic, 80.

Urine: Albumin present with granular and hyaline casts and, on several occasions, numerous red blood cells.

February 7. A blood culture shows Streptococcus viridans after four days' growth. A Wassermann in the blood was negative but positive in spinal fluid. The cell count and result of Noguchi test was not recorded. The temperature continued high with great daily variation (septic type). The pulse gradually increased to 150. The patient became more apathetic. Systolic blood-pressure fell to 82; diastolic to 55. The left leg was edematous. The patient died March 9.

Necropsy: A large area of softening was found in right internal capsule

and corona radiata, and a condition of acute vegetative valvular and mural endocarditis. The mitral valve was nearly filled with large masses of vegetations. There was thrombosis of the left saphenous vein; embolism in the lungs with bronchopneumonia; infarcts in the spleen, and beginning fibrosis in the kidneys. Willow markings were found in the aorta. The fibrosis in the kidneys was perivascular. There was also a focal glomerulonephritis with commencing hyaline degeneration in some glomeruli.

Case XXVI.—J. S., aged nineteen years, a factory operator, entered Ward G, June 5, complaining of intermittent abdominal pain and weakness of ten or eleven weeks' duration. The patient had had diphtheria and scarlet fever when a child and was ill a long while after diphtheria. She had rheumatic fever in 1912, and was in bed six weeks. There was no history of tonsillitis. The family history was negative. The patient went to bed for weakness on April 4. She had intermittent attacks of sharp pain in the lower half of the abdomen, loss of appetite, and occasionally, attacks of vomiting, following the taking of food. She was thin and pale, her face was flushed, her tongue dry, her temperature 103°, pulse 112. The heart was slightly enlarged, the apex in the fifth space 10.5 cm. to the left. A loud, rough, mitral systolic murmur was present with accentuated pulmonary second sound. The murmur was easily heard all over the chest. On June 7, the splenic dulness was slightly increased. The liver was not enlarged. Petechial spots were present in the region of the anterior axillary folds. Hemoglobin, 60 per cent. Red blood cells, 3,200,000; white blood cells, on admission, 11,750. Urine normal.

June 14. Abdominal pain more severe. Both recti moderately rigid. Tenderness over McBurney's point to the lower right costal margin, greatest just below the right costal margin. The left side of the chest lagged on inspiration.

June 14. White blood cells, 16,000. The patient lay on the left side.

June 15. Abdominal symptoms unchanged, tenderness most marked to the left of the umbilicus.

June 17. Abdominal condition is more severe. There is general rigidity. White blood cells, 24,800. An exploratory operation was done and the appendix found to be slightly inflamed and containing an enterolith. It was removed. Nothing else abnormal was found.

June 21. The urine contained albumin, a few casts, white and red blood cells. The patient died June 25, and a necropsy revealed a small patch of fresh vegetations on the mitral valve extending on to the endocardium of the left auricle, embolism of the large branch of the mesenteric artery, with gangrene and perforations of a large portion of the small intestine with general peritonitis. There were infarcts in the kidneys and one in the spleen. Two blood cultures were taken in this case. The first was contaminated, showing streptococcus and Staphylococcus albus. The second showed streptococcus.

METABOLISM STUDIES BEFORE AND AFTER SPLENECTOMY IN CONGENITAL HEMOLYTIC ICTERUS

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In this communication we present the results of a study of the metabolism, before and after splenectomy, in a child five years of age suffering from congenital hemolytic icterus with splenomegaly. As Dr. S. McC. Hamill, to whom we are indebted for the opportunity of making these studies, will, in a later communication, offer a consideration of the clinical and therapeutic problems involved, we will, aside from the metabolic studies, present only a brief abstract of the clinical history, a note on the pathology of the removed spleen and a table (Table I) of the blood examinations before and after operation.

ABSTRACT OF CLINICAL HISTORY

At birth, at term, the child weighed seven pounds and is described as lacking the characteristic red color of the newly born. About twenty-four hours after birth the "alabaster whiteness" of the skin, which the mother describes, changed to a mahogany brown which lasted three months, gradually fading to a sallow pallor, which has persisted. At six months, when the child passed through an attack of pneumonia, it weighed only ten pounds. The general health was poor and gastro-intestinal disturbances frequent. In the

fourteenth month the first severe anemia, accompanied by dark brown discolorations of the skin and preceded by protracted vomiting and diarrhea, was observed. Two months later a similar attack occurred with the new feature of marked edema of the entire body. During these attacks the rectal temperature usually rose to 104 or 105. Periods of recrudescence and exacerbation followed one another until the child was two and one-half years old when an unusually severe attack kept him in bed for five months. Vomiting and diarrhea were severe and hemorrhages from the nose and bowel were frequent and difficult to control. During the second month of this period a partial paralysis of the left side developed. At this time an injection of neosalvarsan was given, more for the hematinic action of the arsenic, than with any suspicion of lues. Gradual improvement followed this treatment and after the paralysis had disappeared, except for a residual spastic palsy of the left leg, the child enjoyed fairly good health. The Wassermann reaction frequently repeated has always been negative. During the eight months following this attack, salvarsan was given five times by rectum. About the time he was five years old and again seven months later, he lost the power of speech, was more or less delirious and complained of pain in his head. At three and one-half and again at four and one-half years, he had an otitis media. His appetite has always been poor, never normal, and at times he refused to eat. A tendency to localized edema, especially of the face and of the hand, has been constantly noted. He tires easily and frequently complains of this. Obstinate constipation has been the rule and the feces are described as dark or orange in color.

From the family history, it is found that a sister was jaundiced for ten days and a brother for two days after birth, but these children, now fifteen and thirteen years of age respectively, have otherwise been in good health. The father is said to have had an enlarged spleen and offers a history of exposure to lues, of skin eruption and chronic abscess of joint and ankle. The mother, three months before the birth of the subject of the present study was paralyzed and suffered a separation of the pelvic bones. The delivery was under anesthesia.

Laboratory Examinations. An examination of the numerous clinical records which have accumulated shows that the urine offers nothing of unusual interest. The only positive finding is an occasional slight trace of albumin. Tests for bile have always been negative and urobilin tests have shown no increase of this substance. Examinations of the feces indicate that food is well digested; tests for occult blood have been negative and no parasites or ova have been found. No records of the early blood examinations have been preserved, except a brief record that at the time of the first severe attack (when fourteen months old) the hemoglobin fell to 24 per cent. and a diagnosis of pernicious anemia was made. A number of counts made during the years 1913 and 1914 showed considerable variation in both hemoglobin (from 65 per cent. to 28 per cent.) and red blood cells (4,180,000 to 1,360,000). The Brulé test and tests for cross hemolysis with normal serum and cells were negative. (These were performed by Dr. E. B. Krumbhaar.) The subsequent blood counts are summarized in Table I.

At the beginning (Dec. 3, 1914) of our metabolism studies one of us (O. H. P. P.) made a complete examination of the child, and from the notes at that time, the following abstract of positive findings has been prepared:

The boy is five and one-half years of age, 105.5 cm. in height, weighs 39 pounds, is well nourished and of good muscular development. His skin is slightly sallow, but there is no true jaundice. Over the vessels of the neck, a systolic bruit is heard and an occasional slight systolic whiff is heard at the apex of the heart. At the base of the heart, the first sound is replaced by a systolic murmur of a blowing character and the second sounds are accentuated. Normal sounds are heard at the tricuspid area. The liver is doubtfully palpable. The splenic dulness begins in the mid-axillary line at the sixth rib and extends down a little below the line of the umbilicus; its greatest length is 18 cm. and its greatest width about 9 cm. The spleen feels firm, smooth and without distinct notches.

The right lower extremity is normal; the left lower extremity normal as to thigh and leg, but the ankle and foot show a spastic paralysis. The urine at this time was amber in color with no gross sediment; the specific gravity was 1.029; tests for albumin, sugar, acetone, diacetic acid, indican and bilirubin were negative. The test for urobilin gave a doubtful reaction; under the microscope some mucus was seen but no cells, casts or crystals. The blood count at this time is given in Table I, under the date of December 3, 1914.

The first metabolic period ran from the fourth to the fourteenth of December and during this time there was little or no change in the patient's condition. Throughout the period there was a tendency to elevation of temperature which, however, rose but once over 101. The child was not kept in bed, ate regularly and required no medication or cathartic. At the end of the period, he was discharged to return after Christmas.

During the interval at home (December 14, 1914, to January 26, 1915), no noteworthy change in condition occurred. On January 26, the patient was readmitted to the University Hospital, service of Dr. Charles H. Frazier. Physical examination revealed nothing new; examination of the blood and urine showed but little change. On January 28, the spleen was removed by Dr. Frazier, under ether anesthesia. The operation was uneventful and there was only a trifling loss of blood. At the time of the operation the coagulation time of the blood was found to be about four minutes and tests for resistance of red cells showed beginning of hemolysis in 0.65 per cent., and complete hemolysis in 0.425 per cent. salt solution. Convalescence after the operation was satisfactory and on February 4, the patient was transferred to the medical service, and the second period of metabolism study was started on February 5. At this time the child's weight was 40 pounds.

On the fourth day of metabolism study, an attack of bronchitis caused a rise of temperature to 103 and for two or three days there was some loss of appetite, and on the ninth day a mild otitis media developed. Despite these disturbances, the metabolism study was continued until the period of ten days representing the eighth to eighteenth days after splenectomy was completed.

At the end of the period, the child's weight was $38\frac{1}{2}$ pounds and he seemed considerably improved in color and strength. The appetite was good. The condition of the bowels demanded an occasional cathartic which, however, never caused watery stools. Even before discharge on February 18, just three weeks after operation, it was evident that a marked improvement in the blood picture had occurred, both hemoglobin and red blood cell count being double that obtained on the first admission.

After discharge, the improvement continued steadily with greatly increased appetite and strength. The skin lost its sallow hue and became normal in appearance. In the two months since operation the child has enjoyed uninterrupted good health except for one attack of indigestion, the result of overfeeding. Two weeks previous to the last blood count given in the table a rather severe nasal hemorrhage occurred as a result of excoriations. The lowered hemoglobin in the last count is probably to be explained by this hemorrhage.

Pathologic Description of the Spleen. The weight is 640 gm.; length 18.3 cm.; width 10.8 cm.; thickness 3.8 at one end increasing to 8.4 at opposite end. The organ is of a uniform bluish-red color. The capsule is for the most part smooth with a few fine adhesions at one pole, where there is also a small circumscribed area (1.5 cm. in diameter) of thickening. The vessels of the hilum are normal. No supernumerary spleens are seen.

On section a large amount of dark fluid blood escapes. The cut surface has a uniform smooth glistening appearance of dull red color. The malpighian bodies are distinctly visible but not so large as in the normal spleen. The trabeculæ are not prominent. The consistence is increased, it being almost impossible to rupture the spleen by pressure with the thumb. At one end (the larger) of the organ is a distinctly circumscribed, but not encapsulated mass (3.5 cm. in diameter), spherical in shape, which shows no malpighian bodies but does present a few minute ochre-colored areas. This area is of the same color and consistence as the rest of the spleen. On section it bulges prominently above the cut surface. The weight of the spleen after escape of fluid blood from three longitudinal incisions is 435 gm.

Gross Diagnosis. Splenomegaly with area of recent infarction.

Microscopic Appearance. Very slight thickening of capsule with no increase of trabeculæ. The sinues are dilated and congested. The reticulum is increased in amount and the cells of pulp appear to be decreased in number. The malpighian bodies show no change except a hyaline thickening of central arteries which is evident in arteries elsewhere. Macrophages are not numerous and deposition of pigment is not seen.

The tumor-like mass described in notes on gross appearance shows intense congestion and hemorrhage without evidence of cell destruction, and represents in all probability the results of occlusion of bloodvessels at time of operation.

Histologic Diagnosis. Congestion, increase of reticulum, hyaline degeneration of arteries. (The rather negative histologic appearance is in general that described for splenomegaly with congenital hemolytic jaundice.)

TABLE I.—BLOOD EXAMINATION BEFORE AND AFTER SPLENECTOMY

Date.	Hb. per cent.	Erythrocytes.	Morphology of erythrocytes.	Reticulated erythrocystes, percentage.	Resistance to sodium chlorid solution.		White blood cells.	Percentage.					
					Partial hemolysis.	Complete hemolysis.		Polys.	Lymphos	Trans.	Monos.	Eosinos.	Basos.
Apr. 13, '14*	60	3,820,000	Poikilocytosis†: polychromatophilia;† occasional normoblasts; anisocytosis†	4.0	0.65	0.425	6,600	41	47.0	...	3	7.0	2.0
June 1, '14*	50	3,450,000	Same as above	6.1	0.6	0.375	9,600	26	72.0	1.0	1	...	...
Dec. 3, '14	23	2,020,000	Same as above; no Howell-Jolly bodies	9.0	0.625	0.375	6,100	49	46.0	3.0	2	...	...
Jan. 26, '15†	33	2,290,000	Same as above	...	0.65	0.425	6,800	54	43.0	...	1	2.0	...
Jan. 28, '15			SPLENECTOMY										
Feb. 3, '15‡	38	3,570,000	Not noted	...	.....	.....	16,600	62	32.0	...	2	4.0	...
Feb. 11, '15‡	45	4,190,000	Morphology much improved; no erythroblasts	...	.....	.....	15,800	70	22.0	3.0	2	2.0	1.0
Feb. 15, '15‡	45	4,480,000	Same as above	...	.....	.....	9,000	44	45.0	...	10	1.0	...
Mar. 9, '15†	75	4,710,000	Normal in appearance; no Howell-Jolly bodies	1.0	0.525	0.35	14,100	56	27.5	7.5	5	2.5	1.5
Apr. 9, '15†	70	5,070,000	Normal	Occasional	0.525	0.325	11,200	41	43.0	4.0	5	6.0	1.0

* Count by Dr. E. B. Krumbhaar. † Count by Dr. O. H. P. Pepper. ‡ Count by hospital intern.

Methods. The child was kept in a private room of the University Hospital, under the constant supervision of one of us (O. H. P. P.) and with a special metabolism nurse in attendance. The complete metabolism study occupied one period of ten days and a supplementary period of five days before splenectomy and a period of ten days after splenectomy. The first period extended from December 3 to December 14, after which the child went home for the Christmas holidays. While at home a supplementary period for the study of uric acid elimination extended from January 20 to January 24. The return to the hospital was delayed on account of the desire of the attendant physicians to improve, if possible, the blood-picture and the general condition. On January 28, two days after readmission, the spleen was removed and on February 5, after a lapse of eight days, the postsplenectomy metabolism studies were begun and continued for ten days. On account of the capricious appetite of the child, it was impossible to adhere to a constant dietary, such as the Folin diet, and therefore considerable liberty was allowed. The intake was determined by weighing all foods taken and analyzing portions for nitrogen and fat. This policy was followed in both of the ten-day periods, but not in the supplementary five-day period when the child was at home. Despite the freedom as to diet, the food intake was quite constant in character from day to day, consisting in the first period essentially of milk, eggs, cereals, apple sauce, bread, crackers, potatoes, butter, sugar, rice, and tapioca. During the first five days of this period, beef, chicken or fish was allowed once a day; during the second five days, these were entirely eliminated, as they were also in the supplementary period of five days before splenectomy and the ten-day period after splenectomy. Thus, except in the first five-day period, the child was on a practically purin and creatin free diet. The calorific value of the diet was adequate. During Periods I and II (Table II) the subject received approximately 1100 calories a day, or about 60 calories per kg. of body-weight. During Periods IV and V the subject was on a slightly lower calorific intake, but entirely adequate, namely, 960 calories per day, or about 50 calories per kg. of body-weight.

The nitrogen of the food was estimated by the Kjeldahl-Gunning

method and the fat by Soxhlet extraction. The urine was collected in twenty-four-hour periods and portions passed during that period were preserved under toluene in an ice-chest. The urine was acid to litmus at all times.

In the analysis of the urine, the total nitrogen was determined by Kjeldahl-Gunning method; ammonia by Folin's[1] method; urea by Benedict's[2] method; uric acid by Folin's colorimetric method;[3] creatin and creatinin by Folin's method[4] and the hydrogen ion concentration according to Henderson's technic.[5]

In the study of the feces the fat content was determined by the Folin-Wentworth method;[6] the iron was estimated by Neumann's method;[7] nitrogen by the Kjeldahl-Gunning method and urobilin by a slight modification of the method recommended by Wilbur and Addis.[8]

Period III (Table II) was considered a desirable control on account of the high figures for uric acid obtained in the first and second periods. The analyses in this period were, therefore, limited to those determinations of special interest in this connection.

In Table II are presented the results of the study of nitrogen metabolism.

Nitrogen Metabolism. During Periods I and II, before splenectomy, the subject was in a slight plus balance. After splenectomy, during Period IV, a great retention of nitrogen occurred, although the intake varied but little from the previous periods and the subject was not gaining in weight. The logical explanation of this change would be either of the following: (1) reparative processes going on in the body, as indicated by the rapid regeneration of hemoglobin and red cells, or (2) the removal of toxic influences leading to an improvement in the general nutritive condition and thus to the normal retention in a healthy child. The utilization of protein was good at all times. The average percentage of total nitrogen eliminated as urea was 85.5 before splenectomy, and 87.2 afterward, figures within the normal range. The differences of the averages may possibly be explained by the changes in one of the other nitrogen constituents of the urine, namely, uric acid.

TABLE II.—METABOLISM IN CONGENITAL HEMOLYTIC ICTERUS BEFORE AND AFTER SPLENECTOMY

Period.	Date.	Wt. in Kg.	Nitrogen intake, Gm.	Urine.										Feces; total nitrogen, Gm.	Total nitrogen output, Gm.	Nitrogen balance, Gm.	Clinical notes and temperature.
				Amt., c.c.	Sp. gr.	Hydrogen Ion Conc.*	Total nitrogen, Gm.	Urea, Gm.	Ammonia, Gm.	Uric acid, Gm.	Total† Creatinin, Gm.	Creatinin, Gm.	Creatin, Gm.				
	Dec. 4, '14	17.7	6.45	480	1.022	6.15	6.09	5.25	0.36	0.468	0.476	0.289	0.217	0.54	6.63	−0.18	98.2
	Dec. 5, '14	....	9.00	530	1.018	5.70	5.46	4.53	0.33	0.468	0.398	0.235	0.154	0.54	6.00	+3.00	98.4
	Dec. 6, '14	....	5.16	480	1.020	5.50	4.99	4.18	0.32	0.468	0.309	0.226	0.096	0.54	5.53	−0.37	101.4
I	Dec. 7, '14	....	5.66	400	1.025	5.85	6.38	5.54	0.26	0.516	0.385	0.270	0.133	0.54	6.92	−1.26	99.6
	Dec. 8, '14	....	6.47	550	1.019	6.15	6.54	5.60	0.32	0.490	0.405	0.261	0.167	0.54	7.08	−0.61	100.2
	Average	....	6.55	488	21	5.87	5.89	5.02	0.32	0.482	0.389	0.256	0.153	0.54	6.34	+0.12	.....
	Dec. 9, '14	....	4.91	280	1.030	6.15	3.96	3.41	0.19	0.410	0.271	0.191	0.093	0.52	4.48	+0.43	99.6
	Dec. 10, '14	....	6.12	500	1.020	6.30	5.18	4.40	0.31	0.544	0.369	0.289	0.093	0.52	5.70	+0.42	100.4
	Dec. 11, '14	....	4.12	270	1.028	6.15	3.00	2.75	0.15	0.544	0.211	0.191	0.023	0.52	3.52	+0.60	99.8
II	Dec. 12, '14	....	5.03	320	1.026	6.00	4.07	3.43	0.20	0.460	0.271	0.241	0.035	0.52	4.59	+0.44	100.2
	Dec. 13, '14	18.2	4.90	360	1.027	6.00	4.98	4.20	0.24	0.788	0.320	0.270	0.058	0.52	5.50	−0.60	98.4
	Average	....	5.02	346	26	6.12	4.24	3.64	0.22	0.549	0.288	0.236	0.060	0.52	4.76	+0.26	.....
	Jan. 20, '15	....	....	440	1.019	....	4.59	....	....	0.400	0.279	0.225	0.063				
	Jan. 21, '15	....	....	410	1.029	....	4.29	....	....	0.560	0.270	0.209	0.071				
	Jan. 22, '15	....	....	415	1.033	....	3.51	....	....	0.520	0.259	0.207	0.060				
III	Jan. 23, '15	....	....	690	1.019	....	3.81	....	....	0.460	0.245	0.215	0.035				
	Jan. 24, '15	....	....	500	1.024	....	4.31	....	....	0.614	0.300	0.270	0.035				
	Average	....	....	491	25	....	4.10	....	....	0.511	0.271	0.225	0.053				

	Jan. 28, '15																
								SPLENECTOMY									
	Feb. 6, '15	18.2	7.08	540	1.023	6.00	5.61	4.95	0.22	0.326	0.300	0.203	0.113	0.35	5.96	+1.12	99.6
	Feb. 7, '15	....	6.23	590	1.020	6.00	4.71	4.08	0.21	0.294	0.283	0.180	0.119	0.35	5.06	+1.17	99.0
	Feb. 8, '15	....	6.41	570	1.020	6.00	4.80	4.16	0.19	0.294	0.311	0.197	0.132	0.35	5.15	+1.26	99.8
IV	Feb. 9, '15	....	4.97	570	1.020	6.70	3.63	3.11	0.12	0.290	0.234	0.176	0.109	0.35	3.98	+0.99	Bronchitis 103.2
	Feb. 10, '15	....	4.99	450	1.023	6.80	3.06	2.68	0.10	0.226	0.194	0.176	0.063	0.35	3.41	+1.58	102.2
	Average	....	5.94	544	21	6.30	4.36	3.80	0.17	0.286	0.264	0.172	0.107	0.35	4.71	+1.22	.....
	Feb. 11, '15	....	6.20	630	1.020	5.70	6.15	5.37	0.31	0.296	0.337	0.287	0.058	0.40	6.55	−0.35	99.4
	Feb. 12, '15	....	5.27	350	1.024	5.50	4.83	4.34	0.23	0.272	0.288	0.203	0.041	0.40	5.23	+0.04	98.8
	Feb. 13, '15	....	4.83	530	1.022	6.00	5.64	4.83	0.31	0.320	0.290	0.253	0.043	0.40	6.04	−1.21	99.0
V	Feb. 14, '15	....	5.38	360	1.023	6.80	4.08	3.54	0 14	0.224	0.238	0.195	0.050	0.40	4.48	+0.90	Otitis media 99.0
	Feb. 15, '15	17.5	6.17	430	1.025	6.70	4.73	4.13	0.18	0.218	0.248	0.203	0.052	0.40	5.13	+1.04	99.0
	Average	....	5.57	460	25	6.14	5.09	4.44	0.23	0.266	0.272	0.228	0.049	0.40	5.49	+0.08	.....

* Expressed as negative logarithms.

† Includes preformed creatinin and creatin as creatinin.

Uric Acid. The uric acid output was exceedingly high in Periods I and II. Period I was not purin free. Period II, however, was practically free from purin intake, notwithstanding which the uric acid output continued on its high level. The urines were highly colored and when allowed to stand gave a precipitate of uric acid crystals. In view of this high elimination of uric acid a supplementary study was made (Period III) during which the subject was again placed on a purin-free dietary, consisting mainly of milk eggs, shredded wheat and custard. In this period the high output of uric acid, presumably almost entirely endogenous, still persisted. This average (Periods II and III), 0.530 gm. of uric acid, is very close to the highest average of uric acid output of an adult on a purin-free diet. Few figures for normal uric acid output in children are to be found in the literature. Closson[9] in a child of about seven years of age found an average output of 0.23 gm. on a purin-free diet.

After splenectomy the average output of uric acid in Periods IV and V decreased 47 per cent. from the average of Periods II and III before splenectomy. It will be remembered that the diets of all these periods were purin free. The appearance of the urine in these later periods was markedly altered, the dark-red color being replaced by a pale yellow, with never a spontaneous precipitate of uric acid.

Hydrogen Ion Concentration. On the same general diet the hydrogen ion concentration of the urine remained constant before and after splenectomy. During Period I, on a mixed diet, an average of 5.87 falls within the average (5.94) of Henderson and Palmer.[10] On the purin-free diet yielding a more alkaline ash, the hydrogen concentration before operation is in agreement with that after the operation. It is of interest here to note that the hydrogen concentration is not appreciably altered by changes in uric acid content of urine, although, as shown by Blatherwick[11] the ability of a urine to dissolve uric acid is a function of the hydrogen ion concentration.

Ammonia Nitrogen. The ammonia nitrogen in our experiments shows no variations from the normal. Its close agreement with hydrogen ion concentration may be noted, thus a rise in the hydrogen ion concentration is associated with a fall in the ammonia output and vice versa.

Creatinin and Creatin. The creatinin output showed a great constancy in Periods II and III, before splenectomy, on the purin-free diet. During Period I, on a mixed diet, the output is slightly above the average of these periods. During Period IV, after the operation, the creatinin output fell to its lowest point, a decrease of 25 per cent. from the average of the other purin-free periods. When the total creatinin, that is preformed creatinin and creatin as creatinin, output of each period is compared, one readily sees that the total creatinin, in all of the periods on creatin-free diet, shows a remarkable constancy. As will be seen from an inspection of the tables, the decrease of creatinin was accompanied by an increase of the creatin amounting to 91 per cent. of the average. Why, in Period IV, the partition of creatinin and creatin changed without any appreciable change of total creatinin is difficult to state. During the last two days of this period the patient suffered from a bronchitis with a rise in temperature, but that these are explanatory factors hardly seems plausible.

As regards creatin output, with the exception of the first period, which was not that of a creatin-free diet, the output shows a fair degree of regularity. The increased output in Period IV has already been pointed out.

There is a paucity of data on the creatinin and creatin output of children on controlled diets. The results obtained by Folin[12] on his children offer figures which may serve for comparison.

The great constancy of our total creatinin (including preformed creatinin and creatin as creatinin) output leads us to believe that for the purpose of comparison in children this is the figure to be used rather than the relative or absolute amounts of creatin or creatinin. This point is now under investigation by one of us (S. G.) and will be reported in a later communication. On the basis of this comparison this total creatinin output agrees very well with other published figures for children. The change in the partition of creatin and creatinin will also be the subject of this later paper. We believe our creatin and creatinin figures to be within the range of normal variations.

Fats. The total intake of fats and the separation of fats in the feces are shown in Table III. In this table Periods I and II represent

the presplenectomy and Periods IV and V the postsplenectomy studies. Each period represents five days.

TABLE III.—FAT DETERMINATIONS

Period.	Total intake Gm.	Total output Gm.	Per cent. of fat utilized.	Total output fatty acids including soaps. Gm.	Per cent. fatty acids in total fat output.	Total output neutral fats.	Per cent. neutral fats in total fat output.
Before splenectomy:							
I	222	8.88	96.01	6.8	76.8	2.1	23.2
II	223	7.57	96.62	5.1	67.0	2.5	83.0
After splenectomy:							
IV	227	13.56	94.04	10.1	74.4	8.5	25.6
V	269	13.55	94.98	9.8	72.3	3.7	27.7

The metabolism of fats shows no abnormal variations. The fat utilization is good, and well within normal limits. As pointed out by Folin and Wentworth,[6] as total fat increases more of that fat is put out as fatty acids (including soaps).

IRON. Table IV presents the results of the examination of the feces for iron. As the iron in human urine seldom exceeds 0.001 mg. the urine is not included. Analyses for iron were made on duplicate samples of dried feces representing periods of ten days, before and after splenectomy, respectively.

TABLE IV.—IRON ELIMINATION IN FECES

Period.	Total intake period Mg. (calculated)	Total output period Mg.	Intake per day Mg.	Output per day Mg.
Before splenectomy				
I				
II	37.69	82.99	3.77	8.29
After splenectomy				
IV				
V	45.61	41.11	4.56	4.11

Thus the first ten days correspond to Periods I and II and the second three days to Periods IV and V. Periods II, IV, and V represent essentially the same diet. The figures for iron intake were calculated from published records[13] of iron content of foods, hence no claim is made for the extreme accuracy of those figures. They merely serve to show that the iron content of the diet agreed very closely and would not account for the large difference in output

Those differences in output before and after splenectomy amounted to about 40 per cent. decrease. That the large output of iron in the period before splenectomy is due to the increased elimination of iron consequent on the excessive destruction of red cells, seems the most plausible explanation. The decreased elimination after splenectomy, with a close agreement of intake and output, show a cutting off of this loss and presumably a return to normal elimination.

Urobilin. Our interest in the urobilin problem has been limited to the influence of the absence of the spleen on the elimination of this substance. In the urine qualitative tests for urobilin gave negative results throughout the experiment. At one time in a concentrated urine a faintly positive reaction was obtained with Ehrlich's reagent. The large bulk of this constituent was in the feces. Because of the small bulk of the child's feces, and the necessity of utilizing considerable portions for other determinations, the use of the wet feces for urobilin determination was impracticable. The feces were therefore dried in the usual way and placed immediately in well-stoppered bottles. At the end of the experiment the feces of Periods I and II, before splenectomy, and IV and V, after splenectomy, were combined for urobilin estimation. In view of the previous work[8] on this substance, it was to be expected that some of the urobilin would be destroyed, or that most of the urobilinogen would be converted into urobilin but whether or not this took place we have no means of determining. The fact remains that considerable urobilinogen was still present at the time of analysis. Inasmuch, however, as both sets of feces were treated alike this was a more or less constant factor. Five gm. of feces were extracted with 100 c.c. of acid alcohol and treated as described in method as outlined by Wilbur and Addis.[8] The dilution for total mass of feces was then calculated. The dilution follows:

Dilution required for extinction of urobilinogen and urobilin absorption bands: Periods I and II (combined) 71,250; Periods IV and V (combined) 7,954.

These results are in accord with those described by Eppinger,[14] who found, in a variety of clinical conditions accompanied by rapid blood destruction, that the urobilin in the stools sank to normal after splenectomy.

Discussion. The literature concerning the relation of the spleen to metabolism may be considered under five heads: (1) studies both before and after splenectomy for disease of the spleen in man; (2) studies in man after splenectomy; (3) studies of congenital hemolytic jaundice; (4) studies of anemia; (5) studies of the effect of removal of the normal spleen in animals.

1. In only three instances have metabolic studies been made both before and after splenectomy for disease of the spleen in man. Two of these are Umber's studies of cases of Banti's disease and the third Minot's study of cases of pernicious anemia. One of Umber's subjects[15] was a boy of fifteen with anemia and icterus. The postoperative period of study covered twelve days and began twenty-four days after the operation. The diet was purin free and a fully controlled metabolic study was made. The results showed no pronounced variation in the distribution of the urinary constituents which could be attributed to the absence of the spleen. Umber makes a point, however, of the fact that after removal of the spleen it was easier to obtain nitrogen equilibrium, attributing the pathologic destruction of protein to a toxic cause. His figures show also a somewhat greater output of purins before the operation than after. In another case of Banti's disease described in this report[15] the "toxic" disturbance of metabolism was not present and splenectomy was not done. In a later study[16] Umber describes a young man of twenty-one, suffering from what he considers as the "toxic" type of Banti's disease. Splenectomy led to striking improvement. The metabolism study of this case was limited to a comparison of total nitrogen intake and output before and after splenectomy. The results confirm his former observation, namely, that a persistent negative balance before splenectomy changes to a positive balance after splenectomy. The postsplenectomy study was made three months after operation. Minot's[17] patient was a colored woman, aged thirty-five, on whom metabolic studies were begun fifteen days after splenectomy and transfusion. The figures given for five twenty-four-hour periods before and six after splenectomy are not for consecutive days. The examination included total nitrogen in urine and feces and urea and ammonia in the urine. The chief results were a change from a slight negative to a slight

positive nitrogen balance and an increase in percentage of urea after splenectomy. The uncertainty of the food intake in the period before splenectomy, the low caloric intake and the shortness of consecutive periods of observation, make these balances of doubtful value.

2. Lo Monaco[18] found in a splenectomized individual no important change in uric acid elimination.

Mendel and Gibson,[19] in the case of a man with enlarged spleen and secondary anemia following malaria, studied the metabolism (total nitrogen, urea, uric acid, ammonia, phosphorus, chlorids and sulphates) after splenectomy, but found no striking variation from the normal distribution of the urinary components. These authors had no pre-splenectomy studies for comparison.

Likewise, Moraczewski,[20] who made some studies of both nitrogenous and mineral metabolism in a man of fifty-one, seven months after splenectomy for "spleen tumor" (malarial), found no important variations. His observations, however, were few in number and were made in the course of an attack of pneumonia which rendered matters of diet and control difficult.

3. The only carefully conducted and complete study of the metabolism in congenital hemolytic icterus is, so far as we are aware, that of McKelvy and Rosenbloom.[21] The patient, a girl aged eleven, on a Folin diet, was studied for six days. The total nitrogen, fat and mineral constituents of the food were determined and both urine and feces studied as to nitrogenous and mineral constituents and the feces as to fat. During a period of six days there was a loss of 4.06 gm. of nitrogen, which the authors suggest may be due to a toxogenic destruction of protein. The nitrogen partition of the urine was normal except in the case of the uric acid nitrogen, which was increased. This increase, the writers state, might be due to the increased liberation of nucleoproteins through hemolysis of the erythrocytes. The study of mineral metabolism showed a loss of sulphur, iron, calcium and magnesium and a retention of phosphorus. The fat metabolism was normal. No metabolism studies were made after splenectomy.

In a woman, aged thirty-nine, with "chronic family jaundice," Tileston and Griffen[22] studied, for three successive days and an added

odd day, the output of ammonia, urea, creatin and creatinin on a purin-free and creatin-free diet. They found the elimination of creatinin and urea to be essentially normal, ammonia somewhat high, and uric acid distinctly increased. However, it should be noted that only one determination of uric acid was made.

Haal[23] in a case of family hemolytic jaundice, found an increased excretion of uric acid and of iron.

4. As the changes in metabolism in various types of anemia have recently been summarized by Minot,[17] we will not present this literature in detail. The opposing views are represented by Rosenqvist and von Noorden. Rosenqvist,[24] in pernicious anemia and bothriocephalus anemia, found variations in nitrogen elimination, with periods of alternate increased and decreased excretion. In bothriocephalus anemia a well-marked loss of nitrogen while the worm was in the body was followed, after removal of the worm, by a retention. Rosenqvist concluded that in both types of anemia a pathologic decomposition of protein is present. Von Noorden[25] opposes this view and as a result of his studies concludes that protein decomposition is not increased as the result of anemia of the ordinary types. The variations in output be believes may be explained by the alimentary and renal disturbances which accompany anemia. That an increased output of nitrogen may occur in anemia due to parasites is admitted, as is also the possibility in non-parasitic anemias of a temporary increase in the output of nitrogen as the result of a sudden destruction of large masses of red cells.

As to uric acid output, von Noorden refers to Rosenqvist's high figures and to other observations and concludes that as a rule in anemia the output is normal but sometimes rises, as in Rosenqvist's work, to twice the normal amount.

It is noteworthy that in bothriocephalus anemia, Rosenqvist found that after removal of the parasite, the purin output increased temporarily and then returned to normal. This temporary increase he explains as due to the regeneration and increased metabolic activity of the blood and somatic cells consequent on the removal of the toxic agent. As the cells recovered their normal equilibrium the output of the purins fell to normal level.

Halpern,[26] studying one case of pernicious anemia and one of splenic anemia, found normal values for the various urinary constituents. His figures for purin output are in no way abnormal.

5. The literature of splenectomy in man for conditions other than chronic anemia, as, for example, gunshot wound, rupture, cyst, etc., shows that no metabolism studies have been made in such conditions. Conclusions concerning the effect on metabolism of removal of the normal spleens in the normal individual must, therefore, be based on observations on animals.

Splenectomy in animals (Paton,[27] Mendel and Jackson,[28] Austin and Ringer,[29] Verzár,[30] Korenchevski[31]) offers no evidence to show that the spleen has an important influence on metabolism, though Richet[32] states that in order to maintain their weight splenectomized animals require a larger quantity of food than do normal animals. In these experiments the dog, and rarely, the cat, were used.

The literature contains no records of the examination of the feces for fat before and after splenectomy. Tileston and Griffen, in one of their cases of chronic family jaundice, studied, without result, the fats of a single stool. McKelvy and Rosenbloom in their case of congenital hemolytic jaundice report normal fat metabolism.

The literature of iron metabolism is, at best, unsatisfactory, and this is especially true of work on the relation of the spleen to iron metabolism. Most of the work is based on Schmidt's[33] conclusions, drawn from the results of the feeding of iron-poor food to normal mice, that the organism possesses great power of conserving the iron and of reutilizing it through some form of intermediary metabolism. In this connection Schmidt regards the liver as the depot for iron from the food, and the spleen as the depot for iron from tissue and erythrocyte catabolism.

On the basis of experiments on splenectomized dogs, Asher and his associates (Grossenbacher[34] and Zimmermann[35]) claim to have demonstrated an increased elimination of iron, often double that of normal animals, at various intervals after splenectomy. These studies were made on young puppies and the observations correspond to periods of a few weeks, two months and ten months after splenectomy.

Austin and Pearce[36], in a series of five dogs in which the iron

elimination was studied before and within two weeks after splenectomy, found a slight increase in iron output in three and practically no change in two. When longer periods had elapsed after splenectomy, as one, nine and twenty months, no evidence was secured of an increase in iron output. Such observations, they concluded, do not support the view that the spleen exerts a constant and important influence on iron metabolism.

No observations in man, on iron elimination before and after splenectomy, are at hand. Bayer[37] in the study of iron elimination after splenectomy for rupture of the spleen and Banti's disease compared his results with those obtained in normal individuals. He found an increased output soon after splenectomy in the case of spleen rupture, but later the elimination returned to normal; in the case of Banti's disease the elimination did not differ from the control. McKelvy and Rosenbloom's studies of congenital hemolytic jaundice before splenectomy show that the elimination of iron in this disease is, on the basis of normal figures in the literature, increased. This increase they explain as due to the great destruction of red cells.

From this brief review of the literature it is evident that in anemia, with or without splenic disease, the majority of investigators have experienced difficulty in obtaining a nitrogen balance. Umber,[15 16] in his study of Banti's disease, Minot,[17] in pernicious anemia, McKelvy and Rosenbloom[21] in congenital hemolytic icterus, and Rosenqvist[24] in pernicious anemia and bothriocephalus anemia all report a pathologic destruction of protein. Umber[15] goes as far as to urge this "toxic destruction" as a criterion for operation. Von Noorden[25] alone opposes this theory of increased destruction of protein in anemia. In the case we report, no difficulty was experienced in obtaining a positive nitrogen balance before the operation; feeding was not forced, the patient merely satisfying his natural desires for food. Nevertheless, the increased retention after the operation on the same nitrogen intake would appear to support the theory that some toxogenic influence had been removed. To this influence, however, must be added as a cause of retention the higher level of reparative processes going on in the body, as, for example, in the bone marrow and possibly other organs. The

difference between our slight positive balance and Umber's marked negative balance before operation may possibly be a difference dependent on the age of the individuals.

Our subject, it will be remembered, was a child, whose natural tendency would be to retain nitrogen for growth, and it is not difficult to imagine that this tendency would affect the toxic destruction to a greater degree than in an adult. (The patients in Umber's cases were fifteen and twenty-one years of age.)

As regards the elimination of uric acid in anemia, with or without disease of the spleen, one finds the general view to be that the elimination is high. Rosenqvist (in 1903) as a result of his studies of pernicious anemia and bothriocephalus anemia, reports large outputs of uric acid, sometimes twice the normal amount. He finds that after the removal of the worm in the latter condition, there is first an increased elimination of purins and then a return to the normal. His explanation for this is an increased metabolic activity of the blood and somatic cells following the removal of the toxic agent. In our case, after removal of the spleen, we found the reverse condition, an immediate drop to normal. That an increase took place between the time of operation and the beginning of our first postsplenectomy period (eight days after operation) we cannot say. When, however, one inspects the results of blood examination after operation, it is observed that the increase in red cells and hemoglobin was steady and gradual, no greater during the first eight days after operation than during the subsequent ten days of our metabolism period; so that regeneration processes were at best gradual.

Umber, in his studies, does not report uric acid output, but groups his findings under total purins of which he found, in Banti's disease, a somewhat greater output before operation than after. Haal, in family hemolytic jaundice, found an increased excretion of uric acid. Von Noorden gives as his opinion, based on a review of the literature, that in anemia the output may be normal, but is sometimes increased. Lo Monaco, and Mendel and Gibson report no change in uric acid excretion after splenectomy but present no presplenectomy studies for comparison.

In congenital hemolytic icterus, McKelvy and Rosenbloom report

higher uric acid output, but present no studies after splenectomy. They give as an explanation for the increased output, the greater formation of nucleoprotein resulting from the destruction of red cells. Their explanation seems to be inadequate, for it is difficult to imagine the destruction of red cells as being the sole source of this large output of purin. It may, to some extent, be a factor, but the toxic influence on the somatic cells generally, of bile products would appear to be a factor of greater importance. The sallow discoloration of the skin in the disease is indication of the general dissemination of substance absorbed from the bile and our knowledge of the toxic influence of bile constituents offers an explanation for a widespread state of cell degeneration and consequent repair which would readily explain the increased output of products of nuclein metabolism.

Our findings concerning the increased elimination of iron before splenectomy are in practical accord with those of McKelvy and Rosenbloom and can be explained as due to the increased blood destruction. Other comparisons are impossible, as in no study before ours has iron elimination been studied both before and after splenectomy. Bayer's studies after splenectomy for spleen rupture and Banti's disease do not include presplenectomy studies but comparisons with normal individuals. In his case of Banti's disease the iron elimination after splenectomy did not differ from that of the normal control; in the cases of spleen rupture a slight increased elimination was followed by a return to normal.

The results of our study of urobilin are in accord with the older views as to the source of this substance, that is excessive blood destruction, and also with the views of Eppinger concerning the decrease of urobilin after splenectomy for various diseases of the blood. It is interesting that in this case of acholuric icterus the mass of urobilin was in the feces and not in the urine.

Summary. In child with congenital hemolytic icterus splenectomy was followed by a disappearance of the discoloration of the skin, a rapid improvement in the condition of the blood and a striking improvement in general health.

Metabolism studies before and after splenectomy gave the following results:

1. A slight positive nitrogen balance before splenectomy was followed by an increased retention eight days after operation.

2. The output of uric acid showed a decrease of 47 per cent. after operation.

3. In the period directly after operation a change in the partition of creatinin and creatin elimination occurred; the total creatinin, however, showing but slight change.

4. Other urinary nitrogen constituents showed no variations from the normal, and no change was found in the hydrogen ion concentration.

5. The utilization of nitrogen was good at all times.

6. Fat metabolism was normal.

7. There was a large loss of iron through the feces before splenectomy followed by a decided decrease (40 per cent.) after operation.

8. The excretion of urobilinogen and urobilin in the feces was markedly diminished after splenectomy; the amount after operation was about one-ninth of that excreted before splenectomy.

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CLINICAL STUDY OF PAIN ARISING FROM DIAPHRAGMATIC PLEURISY AND SUBPHRENIC INFLAMMATION

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In 1911 we reported the results of some experiments on the occurrence and distribution of pain, where the pleural membranes were irritated during the process of removing fluid from the cavity.[1]

We found that the visceral pleura is not sensitive to pressure or scratching of a wire. We found that irritation of the parietal pleura nearly always produced pain, sharp and localized over the area irritated and never referred to distant parts, *e. g.*, the neck and abdomen.

We found the irritation of the diaphragmatic pleura over the outer margin set up pain in the hypochondrium and often in the abdominal wall down to as far as the navel or even to the groin, while over the central portion of the diaphragm it caused pain in the neck, particularly along the trapezius muscle ridge.

From these experiments it seemed justifiable to conclude that the marginal part of the diaphragmatic pleura receives its sensory supply from the lower six intercostal nerves and that the referred pain is attributable to an irritation of the corresponding sensory segments of the spinal cord, which endow the abdominal wall with sensation.

Also that the central portion of the diaphragm receives its sensory nerves from the phrenic nerve, which carries afferent

[1] An Experimental Study of the Pain Sense in the Pleural Membranes, Arch. Int. Med., December, 1911, viii, No. 6, p. 717.

impulses to the cervical cord, and sets up reflex pain in the corresponding spinal segments, namely, the third and fourth cervical.

To supplement these experiments we have observed the character and location of pain in a series of cases in which there was inflammation of the serous membranes lining the upper and lower surfaces of the diaphragm.

Analysis of Sixty-one Cases of Diaphragmatic Pleurisy. During a six-year period sixty-one cases of diaphragmatic pleurisy have been seen and examined by the writer. Such a collection would have been impossible had it not been for the interest and courtesy of the internes and staff of the Cook County Hospital.

Twenty-nine of the cases had a lower lobe pneumonia with associated pleurisy, the remaining thirty-two had pleurisy alone.

Thirty-nine were situated on the right side, twenty-one on the left and one was bilateral. The diagnosis was in most instances made evident by physical findings in the thorax, in four instances confirmed by autopsy, and in six instances abdominal disease was excluded by exploratory laparotomy.

Pain referred to parts distant from the seat of inflammation was the outstanding symptom of these cases. *Referred abdominal pain* was present in fifty-four cases, in all cases involving the upper quadrant (7 to 10 dorsal segments), and in twenty-five cases the lower quadrant as well (7 to 12 dorsal segments). Bilateral pain in the belly was noted four times.

The pain was usually spontaneous and with it was tenderness to pressure. *Hyperesthesia* and *hyperalgesia* of the skin were almost constant and showed a decided tendency to follow band-like areas, corresponding to different spinal segments. Over this sensitive area the *musculocutaneous* reflexes were exaggerated and often the wall remained in a state of rigidity.

The *maximum points* of *pain* and tenderness to pressure were especially studied. (Diagram I.)

This point was located:

(*a*) In the gall-bladder region, 10 times.

(*b*) Lateral to and slightly above the navel, 15 times.

(*c*) Near McBurney's point, 2 times.

(*d*) Over the navel, 1 time.

(*e*) Midepigastrium, 1 time.
(*f*) Splenic region, 1 time.
(*g*) Lumbar region, 2 times.

Referred neck pain occurred in thirty-three cases, or in a little more than one-half of the total. The pain was located by the great majority of patients along the trapezius ridge, occasionally over the shoulder cap and in the supraclavicular space. These areas all are supplied with sensory nerves by the third, and fourth cervical spinal segments.

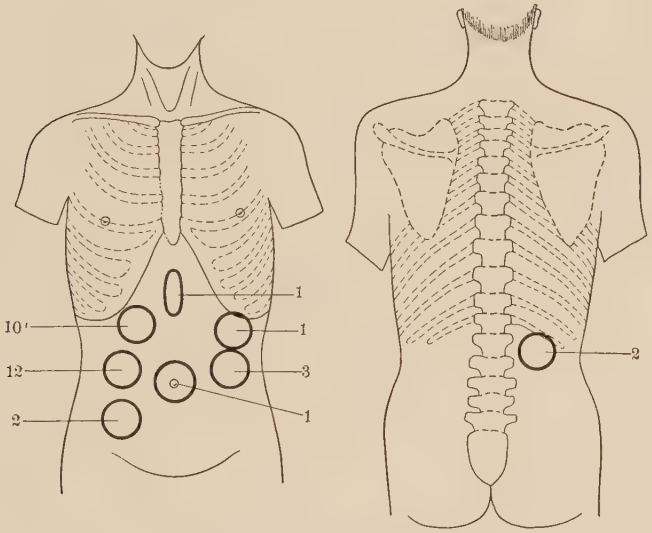

Diagram I.—Points of maximum pain and tenderness in abdomen and back in 61 cases of diaphragmatic pleurisy.

The pain was usually spontaneous and of a sharp stabbing character, always well localized by the patient with the tip of his finger. Pressure over this point was often very painful. The skin and subcutaneous tissues in the immediate neighborhood showed the same hyperplasia and hyperesthesia as were found over the abdomen, but the point of maximum pain and tenderness in the neck was sharply localized, and more constant.

The exact locations of maximum pain points are illustrated in Diagram II.

Factors Influencing Pain. The appearance of referred pains in the abdomen or neck was generally early in the course of the disease. More often abdominal pain preceded the neck pain when both were present. The *duration* of the pain and tenderness varied in much the same way as in parietal pleurisy. Sometimes the pain disappeared after a few hours; as a rule it persisted for one to three days and occasionally for over a week.

The pain was nearly always induced or aggravated by cough and deep inspiration, especially during the acute stage.

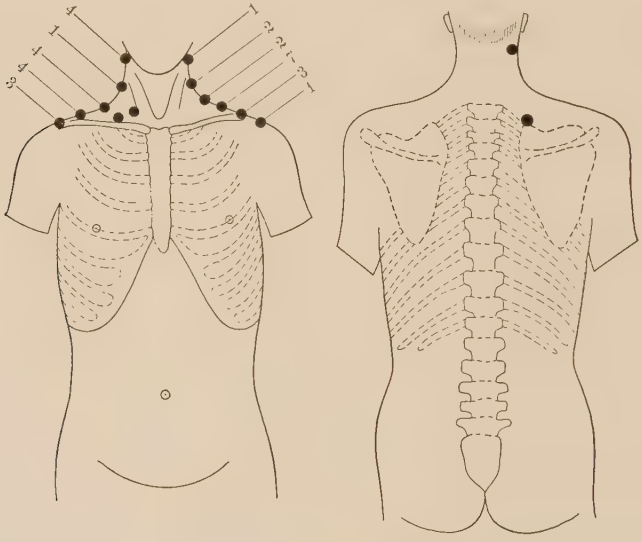

Diagram II.—Points of maximum pain and tenderness in the neck region occurring in 61 cases of diaphragmatic pleurisy.

Measures limiting the excursion of the diaphragm on the affected side, such as lying on the painful side or tight pressure of an abdominal band often gave relief. Some patients secured ease by lying doubled up on the affected side with the shoulder held down by a pillow.

Special Features. The abdominal pain was associated with a maximum point of pain and tenderness far more frequently on the right than on the left side. Such a point was observed in twenty-five out of thirty-six cases on the right side or 70 per cent.;

while it was noted in only seven of eighteen cases on the left side, or 40 per cent.

In contrast to this disparity, the neck pain occurred with almost equal frequency on the two sides. *Tenderness of the phrenic nerve* a symptom emphasized by many writers was found in but one case and that was doubtful. *Vomiting* was present in ten cases and was often responsible for a mistaken diagnosis of abdominal inflammation. *Hiccough* another symptom supposed to be common in diaphragmatic pleurisy was noted in only seven cases, being unusually severe, however, in three.

Does the Referred Pain Originate in the Lung or Pleura? Head, Russell, and others have held that the irritation comes from the lungs, as they question the capability of the pleura to give rise to referred pain. In our series pneumonia of the lower lobe was present with pleurisy in twenty-nine cases. In thirty-two cases pleurisy was present without any signs of consolidation. This indicates that the pleura over the diaphragm does cause referred pain and casts doubt upon the ability of the lung itself to do so. The pleural origin of referred pain is further corroborated by our experiments in which irritation of the lung set up no pain, whereas, irritation of the diaphragmatic pleura gave rise to referred abdominal and neck pain.

Mistaken Diagnoses in Diaphragmatic Pleurisies. *Appendicitis* was incorrectly diagnosed in nine cases. Two of these were operated upon and the abdominal viscera found to be normal.

Cholecystitis was diagnosed in six instances, two of which came to laporatomy without discovering any pathological condition of the gall-bladder or the neighboring structures.

Ulcer of the stomach with perforation was twice diagnosed and once operated upon without discovering any lesion in the belly.

Liver abscess was diagnosed in two patients. One was opened up with negative results. The other mistaken diagnoses included one instance each of *peritonitis, renal calculus, infectious lumbago,* and *brachial neuritis.*

Several of the above-mentioned patients were prepared for operation but were saved by the conservatism of the surgeon. I believe the unusual interest in referred abdominal pain awakened by

frequent discussion of the subject by the Staff of the Cook County Hospital has saved from needless operation many cases that in former years would have been promptly submitted to exploration.

Differentiation of Pain in Diaphragmatic Pleurisy and in Inflammation of Abdominal Viscera. Our knowledge of visceral pain has been so enriched by physiological investigators, more particularly by Hilton, Ross, MacKenzie, Head, Meltzer, Lenander and Hertz, that we should interpret our clinical findings in the light of their results. Without discussing their work in detail, we may recall that Lenander and MacKenzie have maintained that the viscera are insensitive to pain, since during operations under cocaine the stomach, intestine, appendix, gall-bladder, and other organs may be cut, burned, and scratched without producing any painful sensation. All pain proceeding from abdominal inflammation they believe arises from irritation of or traction on the parietal peritoneum, which is supplied with spinal nerve fibers that are specially designed to carry pain stimuli to the cord and brain. The sympathetic nerve fibers supplying the viscera, they say, do not have the power to carry painful stimuli.

These conclusions must be modified by the observations of Kast and Meltzer, who found that the sensibility of the viscera during such operations is appreciably lessened both by the general toxic effect of cocaine and by exposure to the air.

It has been pointed out by numerous investigators that the viscera may be insensitive to the ordinary painful stimuli such as cutting and burning and yet be sensitive to the "adequate stimulus." The adequate stimulus for all the hollow viscera seems to be *tension*. As a result of tension the pain of colic may be explained.

The theory that generally prevails today is that proposed by Ross and supported in essentials by Head, viz., that there are two distinct types of pain in visceral inflammation.

1. *The splanchnic or visceral pain*, which is conveyed directly to the cord and brain by the splanchnic nerves. This pain is, as a rule, dull and deep. A good illustration of this pain is seen in pressure on the testicle or over an inflamed ovary, appendix, or gall-bladder. As a rule, it is localized near the site of its origin.

2. *Somatic or referred pain* is usually located at some distance from the seat of inflammation. It is produced when afferent stimuli from the viscera travel along the splanchnic nerves to the posterior roots of the cord, where they so irritate the corresponding spinal somatic nerves that they give rise to pain in the area of skin and muscles supplied by these nerves.

This pain has a band-like distribution over the trunk and an irregular distribution over the neck, head, and extremities. The pain is in the skin, subcutaneous tissues and muscles and therefore superficial. The sensitized area is hyperesthetic, hyperalgesic and often characterized by painful tender points. The muscular cutaneous reflexes are exaggerated. When the parietal peritoneum is involved then there is direct irritation of the spinal somatic nerves which is similar in kind to referred pain along the same nerves. It is reasonable to expect that both types of visceral and referred pain may be present in visceral inflammation. But clinical experience seems to show that the visceral pain is more constant in abdominal affections than the referred, also that visceral pain may occur alone, *e. g.*, in intestinal colic and some cases of catarrhal appendicitis. Referred pain from the diaphragmatic pleurisy renders painful the spinal nerves supplying the abdominal wall, but the deep visceral pain is not present. Steady deep pressure over the appendix or gall-bladder is well tolerated, whereas in inflammation of these organs deep pressure gives rise to severe deep-seated pain.

The main points of differentiation between diaphragmatic pleurisy and inflammation of the abdominal viscera are as follows:

1. The skin and muscles of the abdomen are more sensitive to pain and touch in referred pleural pain than in visceral disease. This is best elicited by pinching of the wall and scratching of the skin.

2. The cutaneous reflexes are more lively in referred pain than in visceral disease as a rule.

3. Deep pressure with the flat surface of the fingers is well borne in referred diaphragmatic pleural pain, while it elicits a dull, deep pain when applied over an inflamed organ, *e. g.*, an appendix or gall-bladder.

4. Evidences of respiratory infection are often present in diaphragmatic pleurisy, such as cough, expectoration, herpes of lips, sore throat, high leukocytosis, rapid respiration, etc.

5. Appearance of a sharp, definitely localized pain in the neck on the same side as the abdominal pain often reveals the true condition, since it points to irritation of the phrenic nerve.

6. The referred pains in the neck and abdomen are usually induced or aggravated by cough and deep inspiration.

7. Nausea and vomiting are more constant in visceral abdominal inflammation, but may occur and be very pronounced also in diaphragmatic pleurisy.

8. Hiccough is not a very common symptom in diaphragmatic pleurisy, contrary to the current belief. It was present only seven times in our series of sixty-one cases. It is more often seen in visceral diseases of the abdomen than in diaphragmatic pleurisy.

Subphrenic Inflammation. In the study of pain distribution from subphrenic inflammation, we are greatly handicapped. The opportunities for experimental irritation of the under surface of the diaphragm in human beings are rare. Moreover, the existence of abdominal pain in the course of subphrenic inflammation may be properly attributed to associated inflammation of the abdominal viscera. Only in those cases in which definite, sharply localized pain and tenderness develop in the neck or shoulder region, can we be sure that the diaphragm is involved.

We have collected six cases of subphrenic inflammation exhibiting neck pain, three on the left side and three on the right. The painful point is in every respect identical with the referred pain in diaphragmatic pleurisy.

The nerve supply of the peritoneal covering of the diaphragm is probably the same as that of the pleural surface, that is to say, the lower intercostal nerves supply the outer margin, and the phrenic nerves supply the central portion. Hence it is impossible to differentiate between supraphrenic and subphrenic inflammation by the pain alone. The symptomatology and physical findings must also be considered.

THE PRESENT STATUS OF THE ELECTROCARDIOGRAPHIC METHOD IN CLINICAL MEDICINE

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A GALVANOMETER suitable for taking clinical electrocardiograms was designed by Einthoven in 1903. Nine years ago (1906) the method was perfected and became available for general use. The first papers dealing with the results of clinical electrocardiography appeared six and seven years ago (1908 and 1909). The first American papers were published in 1910. This report, then, records the results of observations extending over a period of less than ten years.

The electrocardiogram is a record of the electrical discharges from the heart during its activity. Its chief merit consists in the fact that its form remains constant from a time shortly after birth until the alterations due to old age set in. If it changes at all, it does so as the result of alterations within the heart, or in the position of the heart within the body. An alteration from the accustomed form therefore represents a change which must be looked upon as significant.

A normal electrocardiogram in reality does not exist. A group of normal persons in the prime of life yields electrocardiograms which vary only within certain limits. They tend, naturally, to resemble one another, and from this circumstance an ideal form, regarded as the normal electrocardiogram, has been evolved. The constant form of electrocardiograms depends in part on the fact that the method of obtaining records is free from errors due to

personal equation. If electrocardiograms are taken with a standard instrument, in a standard way, they may be made anywhere by anybody, and should yield identical curves.

The constancy of an individual electrocardiogram, then, is the basis of the method's importance. Compared with any other form of graphic record of circulatory phenomena, this advantage is manifest. No other one is so simple to read. It can be taken without difficulty at any period of life, and without any discomfort to a patient. It cannot, of course, displace other graphic methods when these record activities other than those given in the electrocardiogram. But where information is required which can be obtained by two methods, the electrocardiographic and another, the electrocardiographic is simpler and more reliable.

The well-established form of the so-called normal electrocardiogram is the basis of the value of the abnormal one. The normal one depends on the orderly performance of a number of functions. An abnormal one results when the orderly performance of one or more of these functions is no longer possible. Four main cardiac functions on which the normal curve depends can now be recognized. In the first place it depends on the orderly *passage* of impulses, or more correctly on the orderly spread of electrically excited states through each pair of cardiac cavities, and on the duration of such states in each part of the chambers. It should be noticed that the *production* of impulses cannot be detected in the electrocardiogram, but only the electrical states which the activity of the impulses has initiated. In the second place, the normal electrocardiogram depends on the orderly *sequence* of contraction* of the auricles and ventricles. In the third place, it depends on the orderly *coördination* of the muscular mass in each pair of cavities, and finally on the usual *disposition and volume* of the muscular mass of each pair of cavities. The normal electrocardiogram probably depends on other factors besides these, but these are the ones which we can recognize in the records. The orderly performance of these functions is recognized by the accustomed form and by the time

* We speak of the activity of the cardiac muscle in the usual terms, such as contraction, but it is understood that the accompanying electrical state is the matter of immediate concern.

relation of the waves. The interpretation of functional alterations in the heart is based, therefore, on the alterations which are seen in the electrical elements (*P*, *R* and *T* waves) which represent them.

I take up in turn the factors which determine the normal electrocardiogram and will enumerate what disturbances in cardiac function the curves permit us to detect. The first function mentioned was the normal *passage of the impulse* in each pair of cavities. When the passage is normal through the *auricles*, it is represented (Fig. 1) by a wave (*P*) having a definite rounded

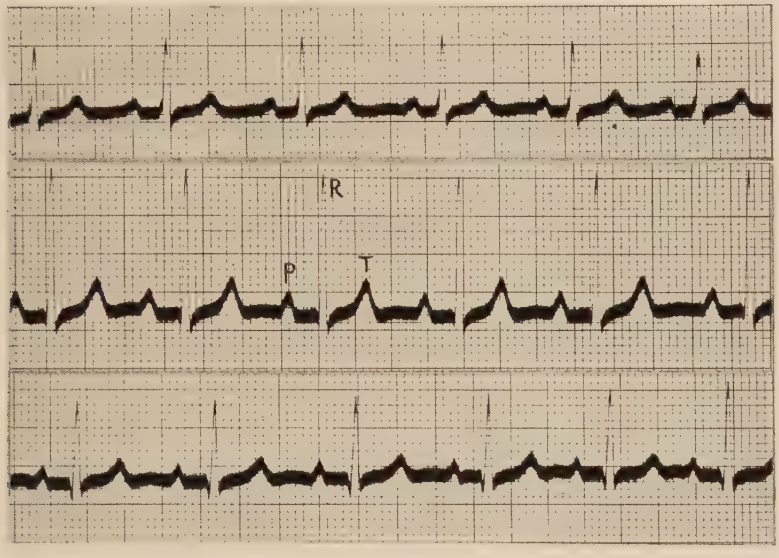

FIG. 1.—Normal electrocardiogram. Leads 1, 2, and 3.

form, a certain duration, and an upward direction.[1] [2] The rate of the heart is shown by the frequency of its regular recurrence. The passage of an impulse having an abnormal origin is detected by an alteration in the form of the wave.[3] The most extreme change is an inversion (Figs. 2 and 3).[4] It is supposed to denote that the impulse has arisen at a lower level of the auricles than usual. If the wave is premature, is out of place, it is called an extrasystole (Figs. 2, 3, 4, and 5). Premature auricular beats are usually followed by ventricular contractions. These often have (Fig. 4),

but need not have (Fig. 5), the same form as the other complexes in the same individual. Many intermediate forms between the inverted and the normal wave occur. It is not yet possible to

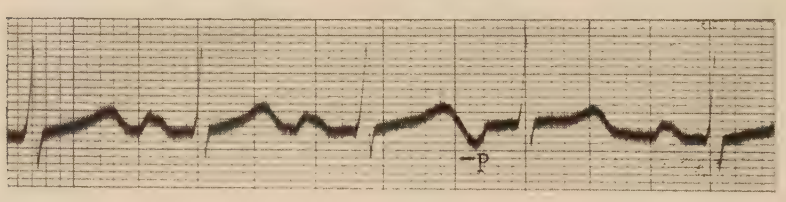

FIG. 2.—In the premature auricular beat (extrasystole) the auricular representative is inverted. Lead 2.

correlate each form with a special method of spread of the impulse. But changes in outline may occur (Fig. 6) without substantial alteration of rhythm.[5] When a given type of abnormal wave recurs

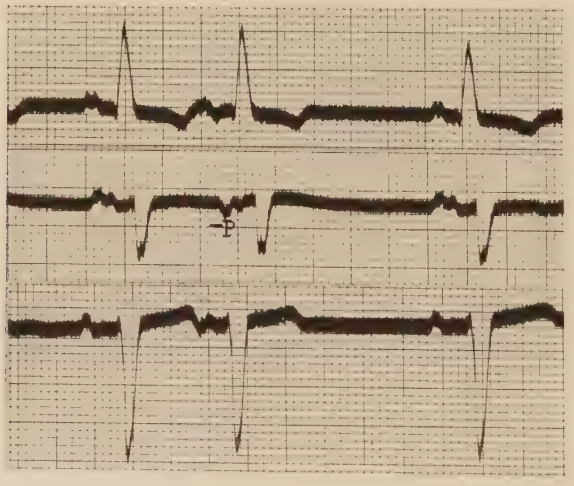

FIG. 3.—A single premature auricular beat taken from each of the three leads is shown. There is a tall *R* wave in L_1; the *R* wave is short and the *S* wave deep in L_2 and L_3. In L_2 the auricular representative is inverted. The ventricular complexes in the extrasystolic cycles are substantially like the usual beats.

in rapid succession, each followed by a ventricular beat, a paroxysm of tachycardia (Fig. 7) exists.[6] [7] The clinical diagnosis depends in addition, of course, on the nature of the onset and offset. These

are the principal auricular changes. In the *ventricles* the passage of a normal wave of excitation is represented by two waves, *R* and

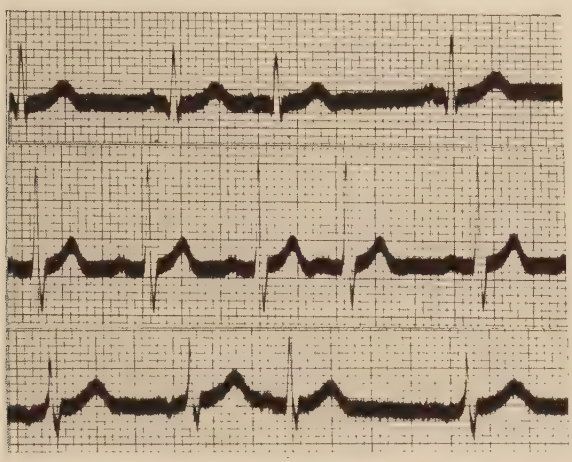

FIG. 4.—A single premature auricular beat taken from each of the three leads is shown. The extra-auricular representatives are like the usual beats. The ventricular complexes are also substantially like the usual beats.

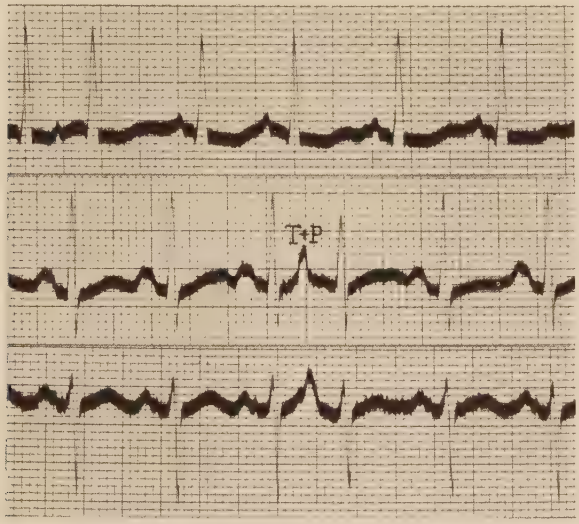

FIG. 5.—A single premature auricular beat taken from each of the three leads is shown. The extra-auricular representatives deform the preceding *T* waves. In L_2 and L_3 the *R* and *S* waves following the extra-auricular beats depart from the usual form.

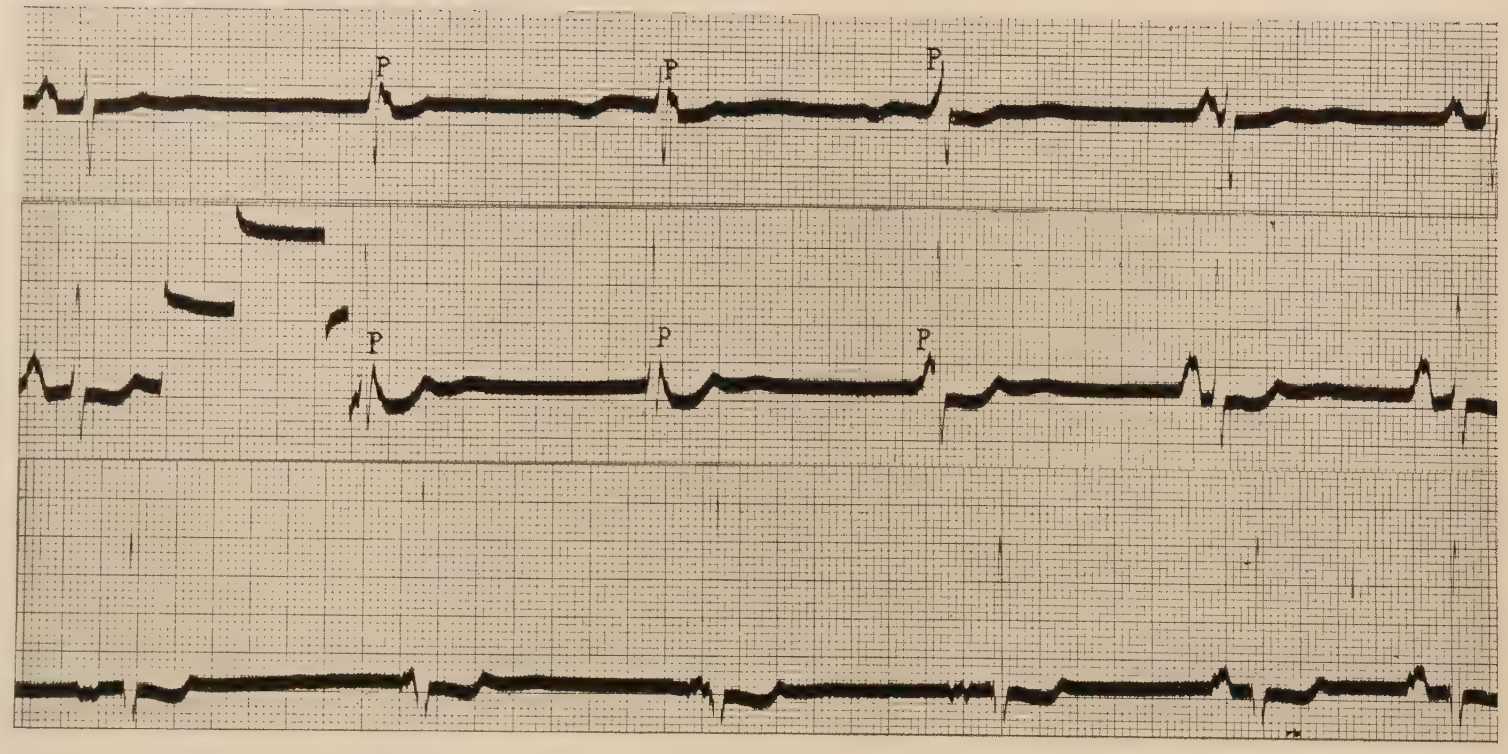

FIG. 6.- A form of nodal rhythm is shown. Leads 1, 2, and 3. Leads 1 and 2 deserve especial attention. They duplicate each other exactly in reproducing an entire phase of the irregularity. The relation of *P* to *R* waves vary in the same manner in each. In L_3 the *P*–*R* relation also varies; the sign of the *P* waves changes gradually from negative at the beginning to positive at the end of the curve. The *P*–*R* time at the beginning is a trifle longer than at the end of the curve. The patient from whom these curves were taken was under the influence of digitalis.

T (Fig. 1), the first a tall spike, the second a shorter but wider, rounded wave, the two separated by a space. Systoles having an

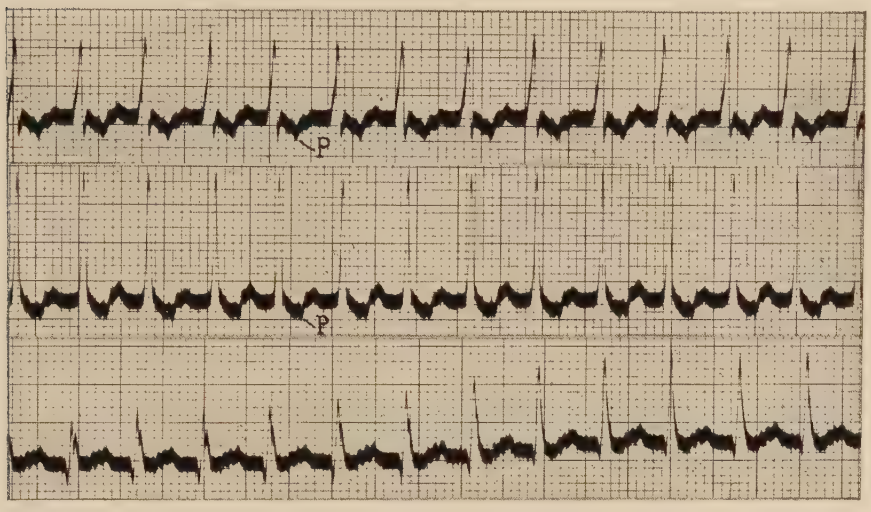

FIG. 7.—A portion is shown of a paroxysm of tachycardia of auricular origin. Leads 1, 2, and 3. The *P* waves in L_1 and L_2 are inverted.

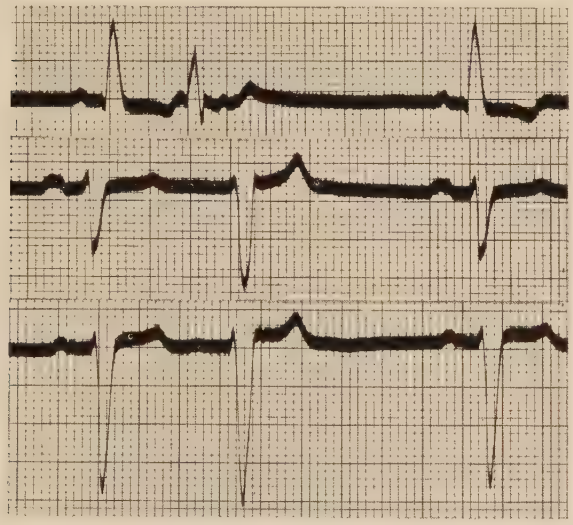

FIG. 8.—A single premature ventricular contraction is shown in each of the three leads. The extrasystole takes its origin in the wall of the left ventricle; there is a tall *R* wave in L_1 and a deep *S* wave in L_2 and L_3.

abnormal origin[8] are detected by an alteration in the form of either of these waves, the altered form depending (1) on the site where the impulse starts, and (2) on the way the excitation wave travels. If it arises in the wall of the left ventricle it has one form (Fig. 8); if in the right ventricle, it has another (Figs. 9 and 10). When a beat of this nature is premature it is called an extrasystole.

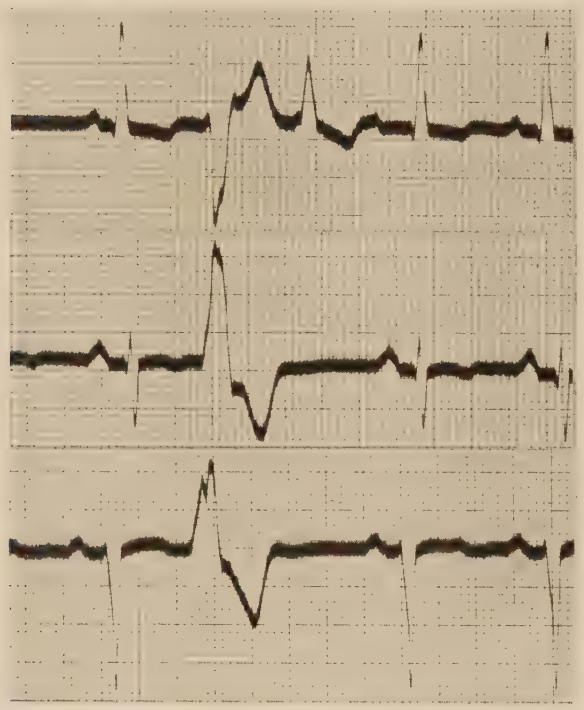

FIG. 9.—A single premature ventricular beat is shown in each of the three leads. In L_1 there is a deep *S* wave; in L_2 and L_3 the *R* wave is tall. In L_1 an added cycle resembling but differing somewhat from the other complexes follows the extrasystole. An explanation of its significance is not entered upon.

A rapid succession of such abnormal beats results in a paroxysm of tachycardia (Fig. 11).[9] Long paroxysms of ventricular origin are rare; usually they consist of a series of not more than twelve to thirty-six beats. In the paroxysm reproduced, two things are clear: (1) that the paroxysm consists of a succession of complexes, precisely like the single extrasystole which precedes it, and (2)

the paroxysm leaves the rate and rhythm of the auricles undisturbed. Another alteration concerns the second ventricular wave, the *T* wave, and consists in an inversion (Fig. 12, *A* and *B*). It occurs under the influence of drugs of the digitalis group[10] and probably other agents.

The second of the factors underlying the normal electrocardiogram is the *sequence of contraction* of the chambers. Disturbance may occur in the regular succession of the activity of the pace-

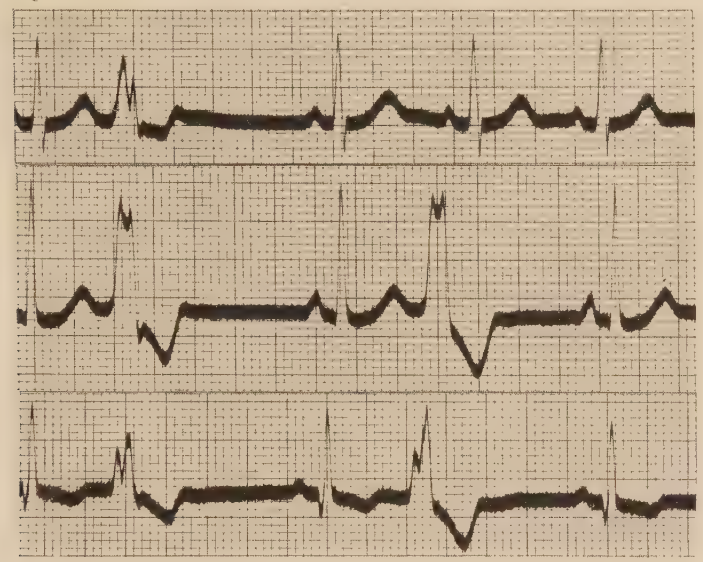

FIG. 10.—Premature contractions in each of the three leads are shown. Here the *R* waves are tall in all the extrasystoles.

maker, as in sinus irregularity (Fig. 13), or disturbance of sequence may occur between the pace-maker (the sinus node) and the auricles, as in sino-auricular block (Fig. 14). Disturbance in sequence occurs also between the auricles and the ventricles (Figs. 15 and 16).[11] These are the familiar heart-blocks, and at rhythmic disturbances require no special description from the electrocardiographic point of view. But certain details of the ventricular mechanism in complete auriculoventricular dissociation have been brought to light by this method. I cite a unique instance. In a case of complete

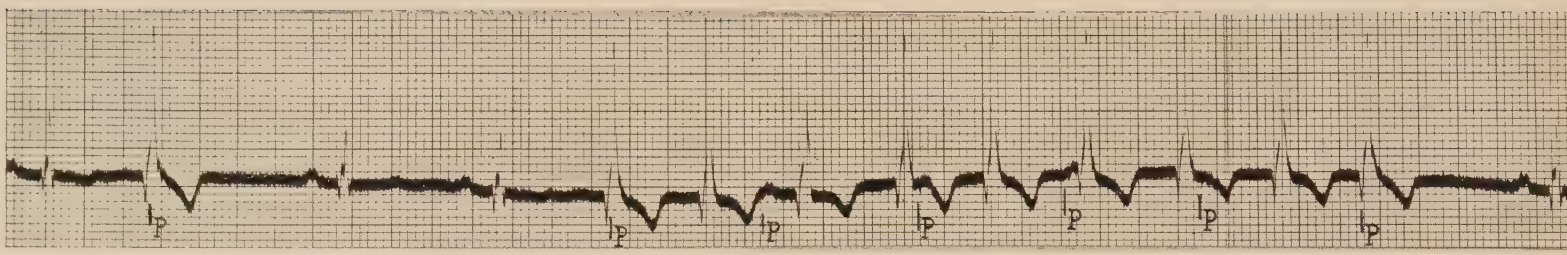

FIG. 11.—A paroxysm of ventricular tachycardia is shown. Lead 3. The paroxysm is composed of a succession of ectopic cycles like the second one reproduced. The paroxysm does not interfere with nor alter the regular recurrence of the auricular beats. Their incidence is indicated in the curve.

FIG. 12 A

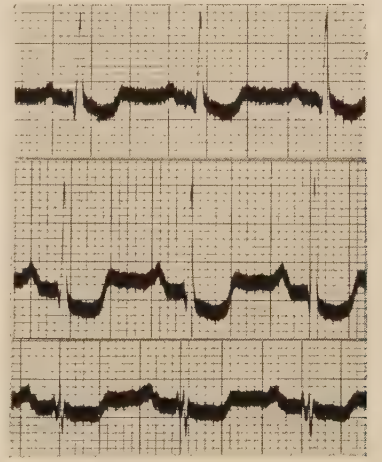

FIG. 12 B

FIG. 12.—*A*, leads 1, 2, and 3 taken from a patient not under the influence of digitalis. The *T* waves are upright. *B*, leads 1, 2, and 3 taken from the same patient under the influence of digitalis. The *T* waves are inverted in the three leads.

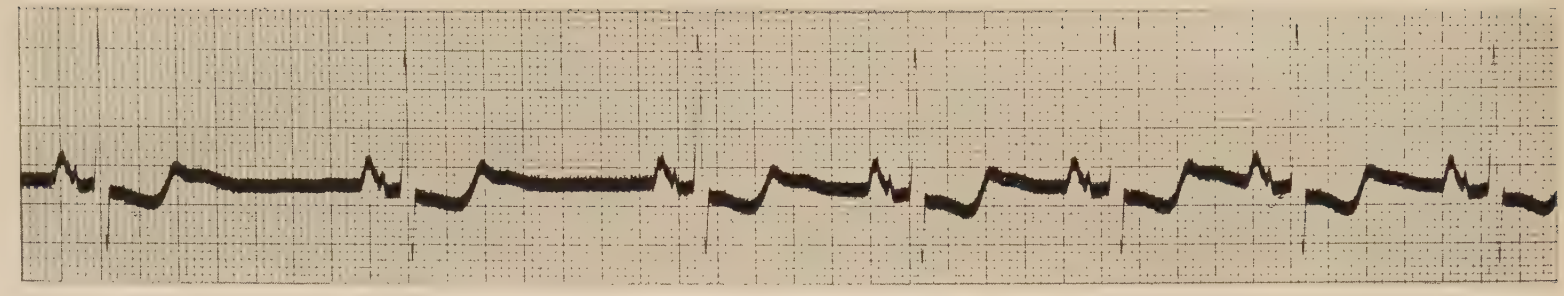

FIG. 13.—Sinus irregularity. Lead 2. The unequal spaces between succeeding cycles are shown.

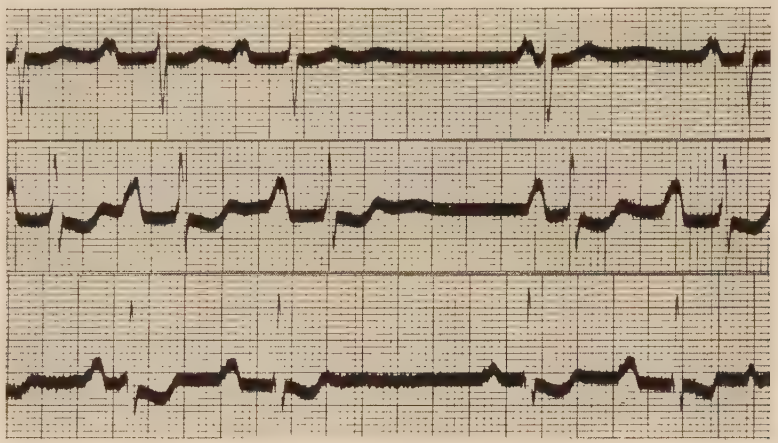

FIG. 14.—Sino-auricular block. Leads 1, 2, and 3. The long intervals between the *P* waves are equal almost to two of the other periods. A moderate sinus irregularity is also present.

heart-block the nature of the ventricular activity changed for a time in an extraordinary manner. It was first of one form (Fig. 17, *A*) and then of another (Fig. 17, *B*). Electrocardiograms like this suggest that under circumstances not completely understood, one part and then another of the conduction system is rendered impassable. If the electrocardiogram returns to a former shape the cause must have been temporary, as in our case. If it does not, the cause is permanent and is probably an anatomical lesion. When the lesion involves one main branch of the A–V bundle, the left branch, for instance, a ventricular electrocardiogram results, having

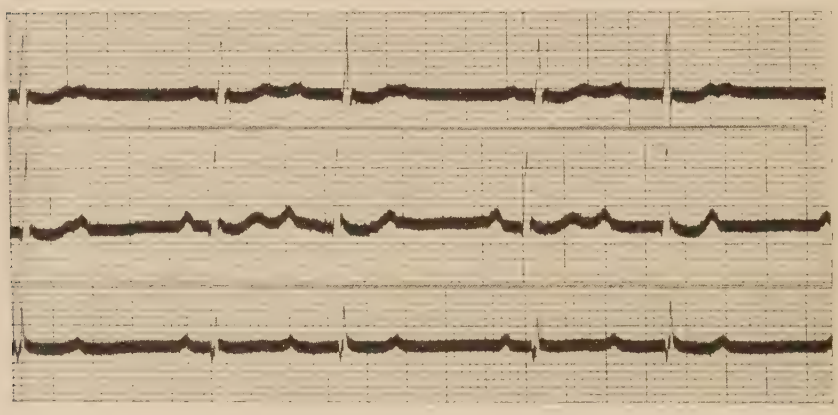

FIG. 15.—Incomplete auriculoventricular block. Leads 1, 2, and 3. The third auricular representative is blocked in each of the three strips. The patient is under the influence of digitalis. The *T* waves are inverted.

a form similar to that which occurs when the impulses spread from the right ventricle (Fig. 17, *A*). When, on the other hand, the right branch is injured the ventricular electrocardiogram is like that which occurs when the impulses spread from the left ventricle (Fig. 17, *B*). More recently electrocardiograms have been collected which, it is supposed, indicate that the main branches or small subdivisions of the bundle have received an injury. The recognition of these complicated forms has become commonplace since the introduction of the electrocardiographic method.[12]

Simpler defects in coördination between the auricles and ventricles also occur. The interval between the contraction of the two may

be lengthened (Fig. 18). But a more interesting form is that in which the interval is shortened and may be changing. A common,

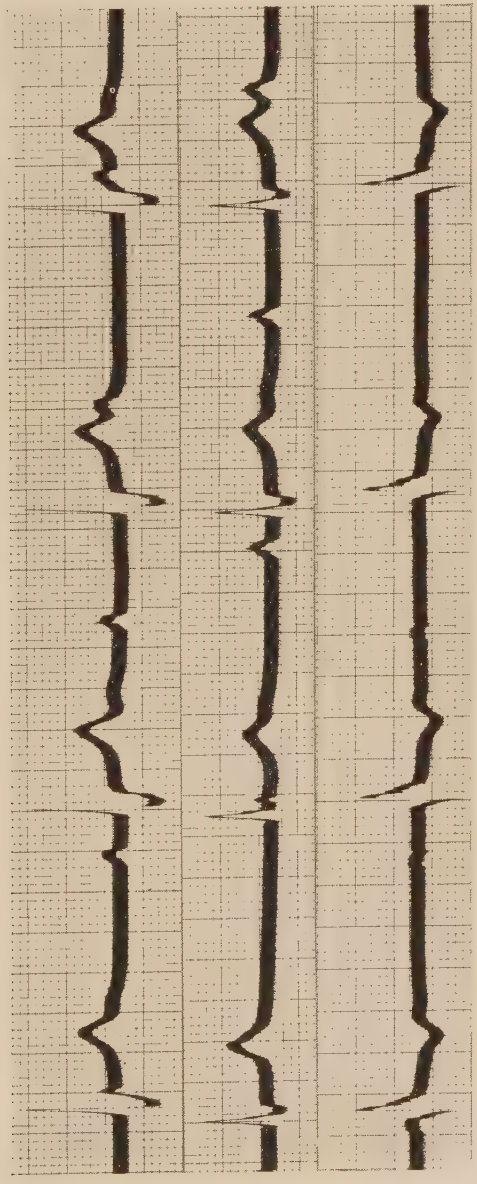

FIG. 16.—Complete auriculoventricular dissociation. Leads 1, 2, and 3. The varying relationship of the *P* waves to the ventricular complexes is shown in many phases.

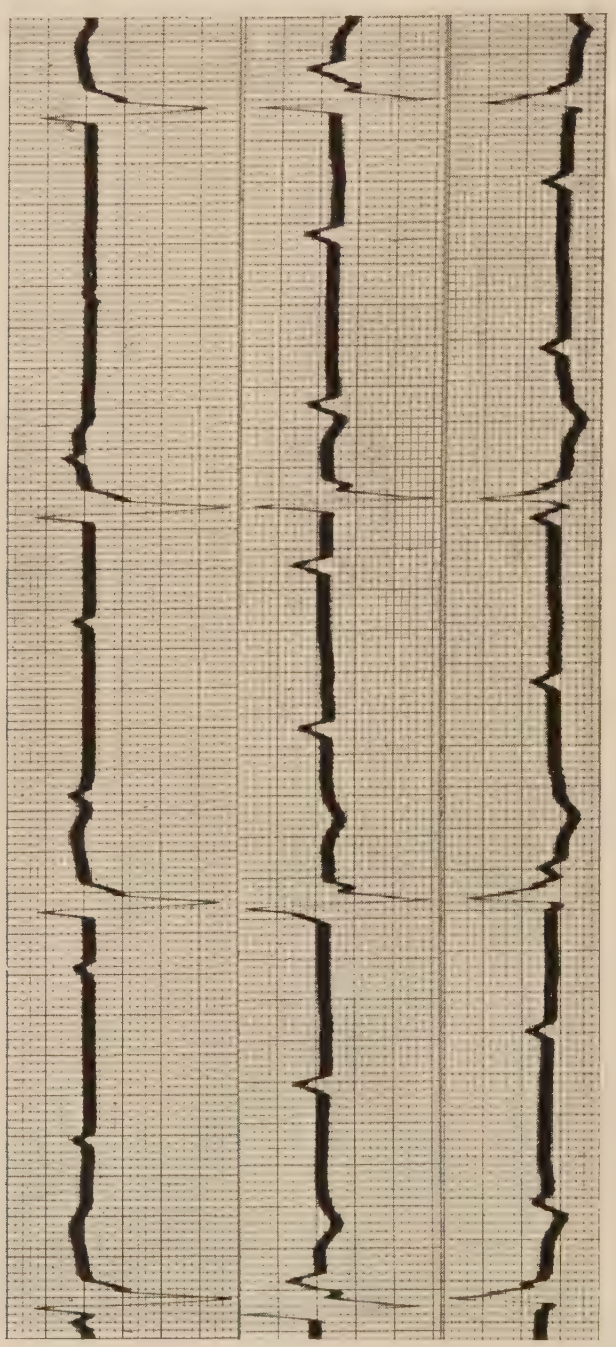

FIG. 17 A.—Complete auriculoventricular dissociation. Leads 1, 2, and 3. The ventricular impulses arise in wall of the right ventricle.

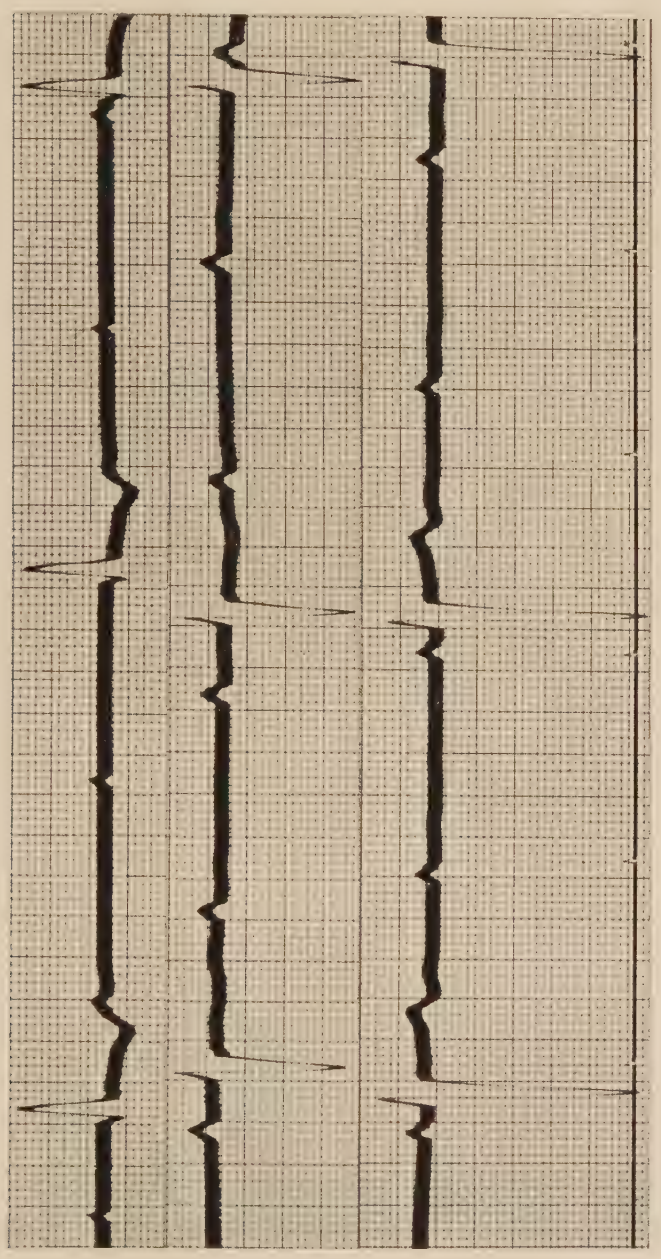

FIG. 17 B.—From the same patient. Leads 1, 2, and 3. The ventricular impulses arise in the wall of the left ventricle.

not necessarily fixed, focus in the junctional tissue provides impulses which are conveyed upward to the auricles and downward to the ventricles. The impulses may reach both synchronously, the cases of true nodal rhythm,[13] or may reach one before the other, or may reach them in an irregular fashion. In the latter event the length of the interval between auricular and ventricular contractions varies (Fig. 6). The mechanism then involves not only disturbance in sequence but also dislocation of impulse formation.

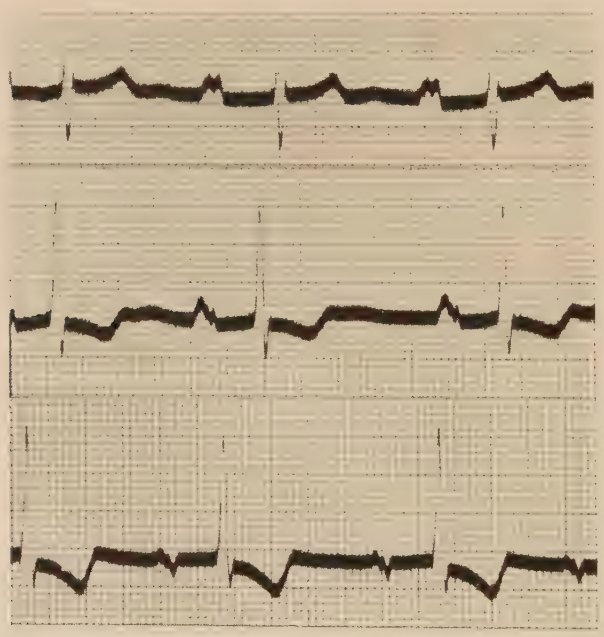

FIG. 18.—Long intervals between the *P* and *R* waves. Leads 1, 2, and 3. In L_1 in the first cycle the interval is 0.4 second. The patient was under the influence of digitalis.

The third factor involved in the production of the normal electrocardiogram is the orderly *coördination of the muscular mass* composing each pair of cavities. The simplest form of disturbance of this mechanism occurs when the form of the auricular (*P*) wave is not rounded above but is split.[14] The two peaks are separated by a deep interval; sometimes the foot-points of the wave are widely separated (Fig. 18). This change has been associated with mitral

stenosis, though it is impossible to say that it may not be found under other circumstances,[15] and has been supposed to depend on a succession in time of the activity of the two auricles as the result of the mitral lesion.

The extreme example of incoördination in the auricles is seen in the completely irregular pulse which is now known to be due to fibrillation of the auricles (Fig. 19). Rothberger and Winterberg and Lewis[16] established this association by their electrocardiographic studies in 1909. The diagnosis of this rhythm is extremely important for it often furnishes the basis of satisfactory treatment not only

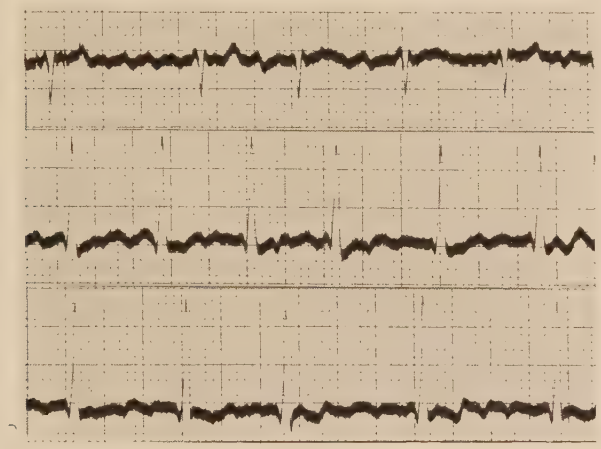

Fig. 19.—Fibrillation of the auricles. Leads 1, 2, and 3. Both fine and coarse waves are seen in the diastolic period.

in ordinary heart failure but in heart failure occurring in pneumonia and probably in other infections.

Flutter[17] (Fig. 20) is another condition which disturbs the orderly beating of the auricles. Its exact mechanism is still unknown, but its significance and treatment is like that of fibrillation. Its detection is more difficult than that of fibrillation because occasionally the pulse remains quite regular. Like fibrillation, it may lead to heart failure on account of the resulting rapid rate of the ventricles. Making the diagnosis is important because treatment is often followed by the same satisfactory result as in fibrillation,

The diagnosis may be made by other than the electrical method, but it is difficult and uncertain. It occurs spontaneously in pneumonia just as does fibrillation, and then gives rise to the same clinical state, and is controlled in the same way.

The failure of orderly coördination of the muscular mass within the ventricles is very much rarer than in the auricles. Two varieties have been described, and both can be detected only by the electrocardiogram. The first is associated with the sort of asynchronism between the two ventricles which, v. Leyden supposed, causes a

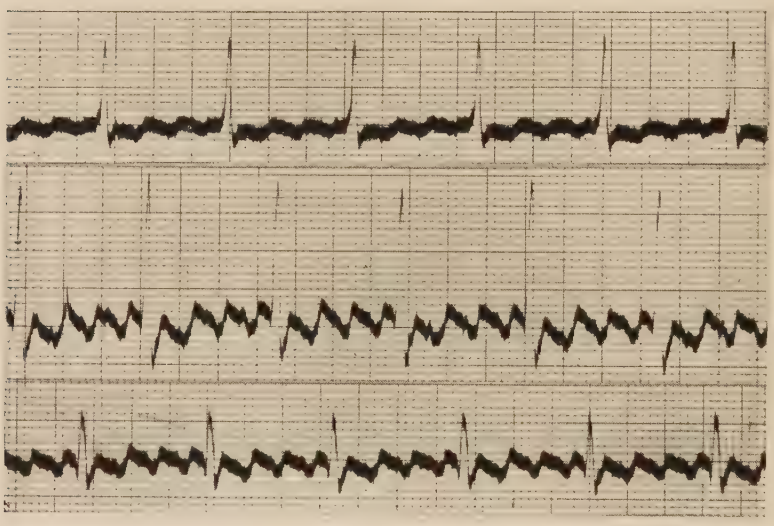

FIG. 20.—Flutter of the auricles. Leads 1, 2, and 3. Regularly recurring auricular representatives at the rate of 360 per minute are seen.

split in the first sound.[12] Experiments and clinical observation, have shown that this occurs in bundle branch lesions. I have already included the electrocardiographic signs of this conditions under disturbances in conduction, where it properly belongs. It is mentioned here because ventricular asynchronism which probably causes the split first sound results from the bundle defect.

A failure of orderly coördination resembling auricular fibrillation also occurs in the ventricles.[18] Its occurrence terminates life. That it is a method of death was suggested by Cushny, but the first

genuine record of its occurrence was obtained by Robinson. There is reason to believe that the onset of this rhythm is responsible for many cases of sudden death, especially in aortic insufficiency.

The fourth factor involved in the production of the normal electrocardiogram is the normal *volume and the usual arrangement* of the muscular mass in each pair of cavities. When these are disturbed, hypertrophy or destruction of the walls of the heart or dilatation of its cavities has taken place, or its position in the chest has altered. These abnormalities undoubtedly cause changes in the electrocardiogram (Fig. 21, *A* and *B*), but a correlation between the change in the heart and the change in the electrocardiogram has not yet been satisfactorily made. We are not in possession of the facts which are necessary before a solution of the problem is possible. Originally[19] electrocardiographic changes were believed to indicate corresponding anatomical alterations, but the electrocardiogram is no longer credited with giving that information. The difficulty has arisen because the electrocardiogram, although it sometimes shows the changes which the roentgenogram leads one to expect, does not *always* do so. The state of the matter is as follows: When the right side of the heart is enlarged, as in mitral stenosis, the ordinary three leads[20] yield ventricular curves, the spike of which is down in L_1 and up in L_3 (Fig. 21, *A*). When the left side of the heart is enlarged, as in aortic insufficiency, the ordinary three leads yield ventricular curves, the spike of which is up in L_1 and down in L_3, and often in L_2 (Fig. 21, *B*). In young children,[21] where the walls of the right side of the heart are relatively large, the curves resemble those of ordinary right-sided enlargement. In cases of congenital[22] cardiac defects, the curves of some resemble preponderant enlargement of one side, the curves of others of the other side. So far the situation is satisfactory, but there are many cases in which we find, for instance, apparently greater left-sided enlargement but fail to find evidence of this in the electrocardiogram. The curves may even be like those seen in right-sided preponderance. The difficulty probably lies in a failure to appreciate what information it is that the electrocardiographic method yields. It does not give an account of the distribution of the muscular mass, but an account of its electrical state. The same arrangement of the mass

of the muscle should, and probably always does, give a curve of the same sort. If it does not, the arrangement of the muscle is probably not precisely that which it is believed to be. When it is remembered that knowledge of cardiac hypertrophy is limited, and that enlargement is usually taken to mean size in terms of the Roentgen-ray appearance, and not in terms of the complicated muscle layers and

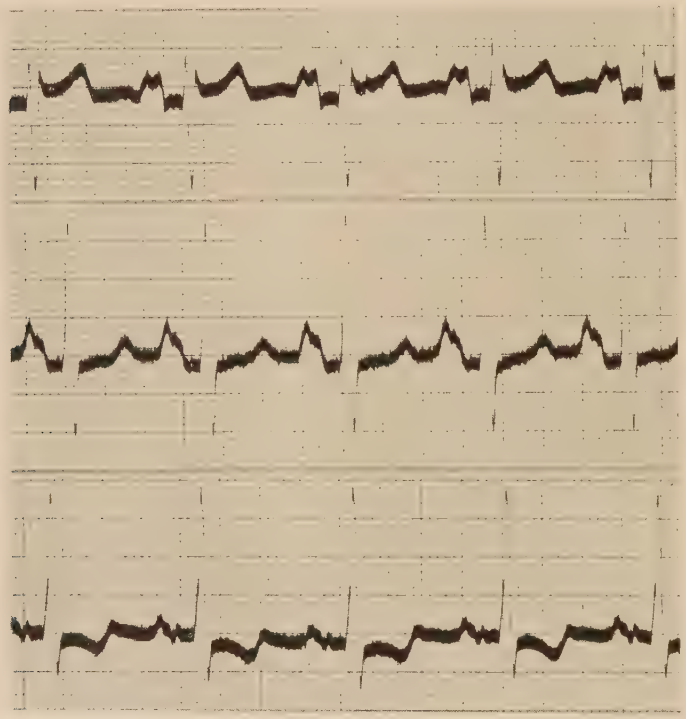

FIG. 21 A.—Curves from a case of mitral stenosis. Leads 1, 2, and 3. Split *P* waves are seen in the three leads; the foot-points of these waves are widely separated. There are short *R* and deep *S* waves in L_1; in L_2 and L_3 the *R* waves are tall and the *S* waves short.

systems of the heart, it is clear why misapprehensions arise. The muscle layers of the heart are, in fact, not coextensive with a single cavity. They probably are strained and injured differently in different valve lesions, and the variations probably determine the shape, size, and constitution of the layers. The altered layers one may easily believe, alter the electrical values with which we are

immediately concerned. Investigations, keeping these muscular balances and their electrical equivalents in view, may lead to a solution of the difficulty.

Alterations of the topography of the heart in the chest, due to displacements resulting from accumulations of fluid or air in the pleura or to dislocations resulting from adhesions, are responsbile

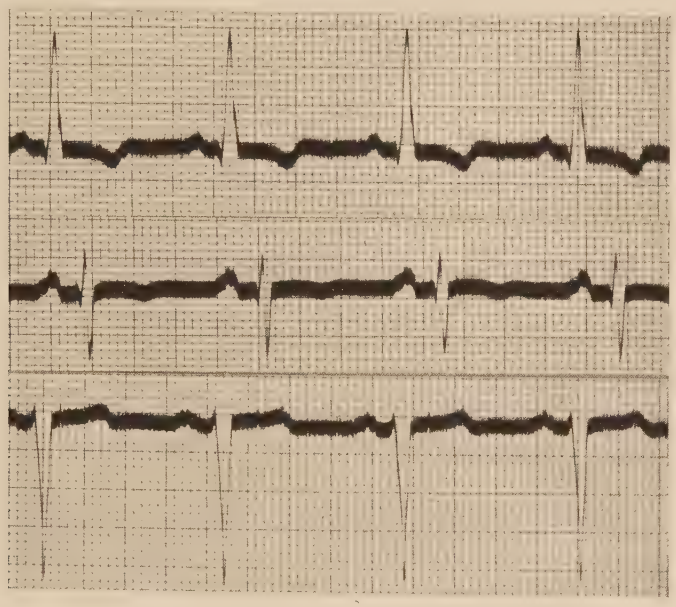

FIG. 21 B.—Curves from a case of cardiosclerosis. In L_1 there are tall R waves. In L_2 the R waves are shorter and moderate-sized S waves appear. In L_3 there are small R waves but deep S waves.

for changes in the electrocardiogram as yet ill defined.[23] Transposition of the heart (dextrocardia)[24] is readily distinguished from displacements by this method. The electrocardiogram, lead for lead, is reversed; to be normal the usual first lead must be taken from left arm to right arm; the second lead from left arm to right leg; the third lead from right arm to right leg.

The galvanometric method has also been used for recording heart sounds.[25] These have been registered by this method better than by any other so far used. The record is especially valuable when it is

combined with the electrocardiogram by means of a two-string galvanometer or by a second instrument. It is unnecessary to describe the method or its results in detail. It has illuminated a number of questions which have been of interest in auscultation, especially in relation to the auricular systolic murmur in mitral stenosis and its fate when the auricles fibrillate. It has illuminated these questions, but it has contributed nothing new in principle.

It was anticipated, unwisely, that the method would also contribute toward an estimation of the work power of the heart, of its functional efficiency. From this point of view, electrocardiography has been disappointing. But the development of electrical potential, of which the galvanometric method gives information, is only one of the functions of muscular activity. An account of a single function may, naturally, on occasion, be an index of the entire activity of a tissue. But the estimation of electrical discharge has so far not been such an indicator. More detailed observation and closer analysis may indicate capacities which are not yet appreciated.

The description of the normal electrocardiogram and its principal alterations observed in clinical medicine is thus concluded. When the subjects reviewed are grouped under the topics familiar in cardiac pathology, they are seen to be included under headings of irregularities in mechanism, hypertrophy and dilatation, and malpositions and displacements. To these subjects the method has yielded added information. We are now able to think of mechanism in greater detail, as in fibrillation and flutter. Asynchronism of the chambers can now probably be demonstrated. The exact origin and method of the passage of impulses has become a matter of importance, as in paroxysms of tachycardia. In the detailed study of individual waves, notice is taken of alterations which are of consequence in treatment, as in the *T* wave changes arising under the influence of digitalis. In recognizing the value of small alterations of this kind it has become clear that each change in the electrocardiogram may be a change of significance, and may not be dismissed as of no importance.

I have in this review collected data which may be grouped under four headings: (1) those relating to arrhythmias, the mechanism of which has been brought to light by the electrical method; (2)

certain facts relating to the *passage of impulses* through the auricles and ventricles, a knowledge of which is being increasingly valuable in diagnosis and in treatment; and (3) certain considerations in regard to the *size* of the heart and (4) its position in the chest.

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